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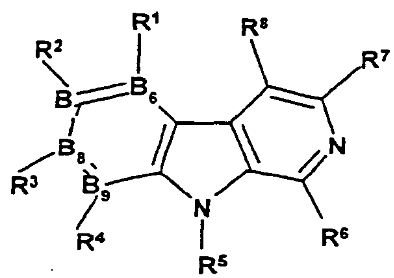
(54) **Substituted beta-carbolines as IkB kinase inhibitors**

(57) Compounds of the formula I



(I)

are suitable for the production of pharmaceuticals for the prophylaxis and therapy of disorders in whose course an increased activity of NFκB is involved.

EP 1 134 221 A1

Description

[0001] The invention relates to novel substituted beta-carbolines, a process for their preparation and use thereof as pharmaceuticals.

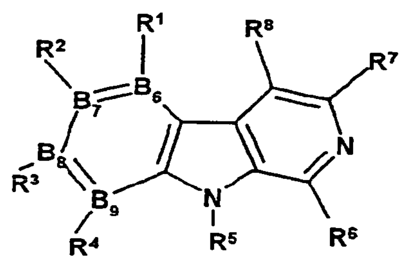
[0002] United States Patent 4,631,149 discloses beta-carbolines useful as antiviral, antibacterial and antitumor agents. United States Patent 5,604,236 discloses beta-carboline derivatives containing an acidic group, useful as thromboxane syntheses inhibitors.

[0003] NFkB is a heterodimeric transcription factor which can activate a large number of genes which code, inter alia, for proinflammatory cytokines such as IL-1, IL-2, TNFα or IL-6. NFkB is present in the cytosol of cells, building a complex with its naturally occurring inhibitor IkB. The stimulation of cells, for example by cytokines, leads to the phosphorylation and subsequent proteolytic degradation of IkB. This proteolytic degradation leads to the activation of NFkB, which subsequently migrates into the nucleus of the cell and there activates a large number of proinflammatory genes.

[0004] In disorders such as rheumatoid arthritis (in the case of inflammation), osteoarthritis, asthma, cardiac infarct, Alzheimer's disease or atherosclerosis, NFkB is activated beyond the normal extent. Inhibition of NFkB is also of benefit in cancer therapy, since it is employed there for the reinforcement of the cytostatic therapy. It was possible to show that pharmaceuticals such as glucocorticoids, salicylates or gold salts, which are employed in rheumatic therapy, intervene in an inhibitory manner at various points in the NFkB-activating signal chain or interfere directly with the transcription of the genes. The first step in the signal cascade mentioned is the degradation of IkB. This phosphorylation is regulated by the specific IkB kinase. To date, no inhibitors are known which specifically inhibit IkB kinase.

[0005] In the attempt to obtain active compounds for the treatment of rheumatoid arthritis (in the case of inflammation), osteoarthritis, asthma, cardiac infarct, Alzheimer's disease, carcinomatous disorders (potentiation of cytotoxic therapies) or atherosclerosis, it has now been found that the benzimidazoles according to the invention are strong and very specific inhibitors of IkB kinase.

[0006] The invention therefore relates to the compounds of the formula I



(I)

and/or a stereoisomeric form of the compounds of the formula I and/or a physiologically tolerable salt of the compounds of the formula I,
where B_6, B_7, B_8 and B_9 are independently selected from the group consisting of carbon atom and nitrogen atom, where B_6, B_7, B_8 and B_9 together are no more than two nitrogen atoms at the same time;
where the substituents R^1, R^2, R^3, R^4 and R^8 independently of one another are

1. hydrogen atom,
2. halogen,
3. -OH,
4. -CN,
5. sulfo,
6. $-NO_2$,
7. $-NH_2$,
8. alkoxy,
9. substituted amino,
10. -COOH,
11. $-O-R^{10}$, wherein R^{10} is alkyl, substituted alkyl or aryl,
12. $-C(O)-R^{12}$, wherein R^{12} is alkyl, substituted alkyl or aryl,
13. $-C(O)-O-R^{12}$, wherein R^{12} is as defined above,
14. aryl,
15. -O-aryl,
16. substituted aryl,

17. -O-substituted aryl,
18. alkyl,
19. substituted alkyl,
20. $-CF_3$ or
21. $-CF_2-CF_3$,

provided that at least one of R^1, R^2, R^3, R^4 and R^8 is not a hydrogen atom,

R^5 is

1. hydrogen atom,
2. alkyl,
3. alkyl radical, substituted at one or more positions by one or more of the radicals, halogen, amino or hydroxyl,
4. $-C(O)-R^9$ or
5. $-S(O)_2-R^9$, in which
   R^9 is

   a) alkyl,
   b) alkyl radical, substituted at one or more positions by one or more of the radicals, halogen, amino or hydroxyl,
   c) aryl,
   d) aryl radical, substituted at one or more positions by one or more of the radicals, halogen, amino, or hydroxyl,
   e) $-NH_2$,
   f) alkoxy or
   g) substituted amino, and

R^6 and R^7 independently of one another are

1. hydrogen atom,
2. halogen,
3. -OH,
4. methyl,
5. $-O-(C_1-C_{10})$-alkyl, wherein alkyl is unsubstituted or mono- to trisubstituted independently of one another by

   5.1 aryl,
   5.2 halogen,
   5.3 $-NO_2$,
   5.4 sulfo,
   5.5 -COOH,
   5.6 $-NH_2$,
   5.7 $-O-(C_1-C_4)$-alkyl or
   5.8 -OH, or

6. $-N(R^{13})_2$, wherein R^{13} is independently of one another hydrogen atom, aryl, $-C(O)-(C_1-C_4)$-alkyl or substituted aryl or alkyl, wherein alkyl is unsubstituted or mono- to tri- substituted independently of one another as defined under 5.1 to 5.8, or R^{13} together with nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,

provided that a compound of the formula I, where R^1 is Br, R^2 is $-O-C(O)CH_3$, R^5 is $-C(O)CH_3$, R^3, R^4, R^6, R^7 and R^8 together are each hydrogen atom and B_6, B_7, B_8 and B_9 together are each carbon atom is excluded; a compound of the formula I, where R^2 is $-O-C(O)CH_3$, R^3 is Br, R^5 is $-C(O)CH_3$, R^1, R^4, R^6, R^7 and R^8 together are each hydrogen atom and B_6, B_7, B_8 and B_9 together are each carbon atom is excluded; a compound of the formula I, where R^2 is Br, R^1, R^3, R^4, R^5, R^6, R^7 and R^8 together are each hydrogen atom and B_6, B_7, B_8 and B_9 together are each carbon atom is excluded; a compound of the formula I, where R^3 is Br, R^1, R^2, R^4, R^5, R^6, R^7 and R^8 together are each hydrogen atom and B_6, B_7, B_8 and B_9 together are each carbon atom is excluded

[0007] Preferred are compounds of formula I, wherein

B_6, B_7, B_8, and B_9 are each a carbon atom,
R^1, R^2, R^3, R^4 and R^8 independently of one another are

1. hydrogen atom,
2. halogen,
3. -CN,
4. -COOH,
5. $-NO_2$,
6. $-NH_2$,
7. -O-(C_1-C_{10})-alkyl, wherein alkyl is mono- to penta- substituted independently of one another by

    7.1 phenyl, which is unsubstituted or mono- to pentasubstituted by halogen or -O-(C_1-C_4)-alkyl,
    7.2 halogen,
    7.3 $-NH_2$,
    7.4 -OH,
    7.5 -COOH,
    7.6 $-NO_2$,
    7.7 $-S(O)_y-R^{14}$, wherein y is zero, 1 or 2, R^{14} is -(C_1-C_{10})-alkyl, phenyl, which is unsubstituted or mono- to penta-substituted as defined for substituents under 7.1 to 7.9, amino or $-N(R^{13})_2$,
    wherein R^{13} is independently of one another hydrogen atom, phenyl, -(C_1-C_{10})-alkyl, -C(O)-(C_1-C_7)-alkyl, -C(O)-phenyl, -C(O)-NH-(C_1-C_7)-alkyl, -C(O)-O-phenyl, -C(O)-NH-phenyl, -C(O)-O-(C_1-C_7)-alkyl, $-S(O)_y-R^{14}$, wherein R^{14} and y are as defined above,
    and wherein alkyl or phenyl in each case are unsubstituted or mono- to penta- substituted independently of one another as defined under 7.1 to 7.9 above, or
    R^{13} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,
    7.8 -O-(C_1-C_{10})-alkyl or
    7.9 -O-phenyl,

8. $-N(R^{13})_2$, wherein R^{13} is as defined in 7.7 above,
9. -S(O)y-R^{14}, wherein R^{14} and y are as defined in 7.7 above,
10. -C(O)-R^{12}, wherein R^{12} is phenyl or -(C_1-C_7)-alkyl, wherein alkyl or phenyl are unsubstituted or mono- to penta- substituted independently of one another as defined under 7.1 to 7.9 above,
11. -C(O)-O-R^{12}, wherein R^{12} is as defined in 10. above,
12. -(C_1-C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to pentasubstituted independently of one another as defined under 7.1 to 7.9 above,
13. $-CF_3$ or
14. $-CF_2-CF_3$,

provided that at least one of R^1, R^2, R^3, R^4 and R^8 is not a hydrogen atom,

R^5 is

1. hydrogen atom,
2. -(C_1-C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to pentasubstituted independently of one another as defined under 7.1 to 7.4 above,
3. -C(O)-R^9, wherein R^9 is
    $-NH_2$, -(C_1-C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to penta- substituted independently of one another as defined under 7.1 to 7.4, or $-N(R^{13})_2$, wherein R^{13} is as defined in 7.7 above, or
4. $-S(O)_2-R^9$, wherein R^9 is as defined in 3 above, and

R^6 and R^7 independently of one another are hydrogen atom or methyl, provided that a compound of the formula I where R^2 is Br, R^1, R^3, R^4, R^5, R^6, R^7 and R^8 together are each hydrogen atom is excluded and a compound of the formula I, where R^3 is Br, R^1, R^2, R^4, R^5, R^6, R^7 and R^8 together are each hydrogen atom is excluded.

[0008] More preferred are compounds of formula (I) wherein

B_6, B_7, B_8, and B_9 are each a carbon atom,
R^1, R^2, R^3 and R^4 independently of one another are hydrogen atom, halogen, cyano, nitro, amino, -O-(C_1-C_7)-

alkyl, phenyl, -O-phenyl, $-CF_2-CF_3$, $-CF_3$, $N(R^{13})_2$,

wherein R^{13} is independently of one another hydrogen atom, $-(C_1-C_7)$-alkyl, phenyl, -C(O)-phenyl, -C(O)-NH-phenyl, -C(O)-O-phenyl, $-C(O)-O-(C_1-C_4)$-alkyl, $-C(O)-(C_1-C_7)$-alkyl or $-(C_1-C_{10})$-alkyl, wherein alkyl or phenyl are unsubstituted or mono- to trisubstituted independently of one another as defined under 7.1 to 7.9, or R^{13} together with nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,

$S(O)_y-R^{14}$,

wherein y is zero, 1 or 2, and R^{14} is $-(C_1-C_{10})$-alkyl, phenyl, which is unsubstituted or mono- to pentasubstituted as defined for substituents under 7.1 to 7.9, amino or $-N(R^{13})_2$, wherein R^{13} is as defined above,

wherein alkyl is unsubstituted or mono- to tri- substituted independently of one another as defined under 7.1 to 7.9, or

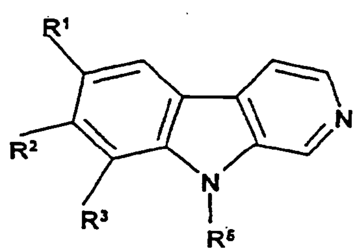
$-C(O)-O-R^{12}$, wherein R^{12} is as defined above,

R^6, R^7 and R^8 independently of one another are hydrogen atom, methyl, amino, $-N(R^{13})_2$, wherein R^{13} is as defined above, provided that at least one of R^1, R^2, R^3, R^4 and R^8 is not a hydrogen atom, and

R^5 is as defined above,

provided that a compound of the formula I where R^2 is Br, R^1, R^3, R^4, R^5, R^6, R^7 and R^8 together are each hydrogen atom is excluded and a compound of the formula I, where R^3 is Br, R^1, R^2, R^4, R^5, R^6, R^7 and R^8 together are each hydrogen atom is excluded.

[0009] Even more preferred are compounds of formula (II)



(II)

and/or a stereoisomeric form of the compounds of the formula II and/or a physiologically tolerable salt of the compounds of the formula II, wherein;

R^1, R^2 and R^3 are independently of one another hydrogen atom, halogen, cyano, amino, $-O-(C_1-C_4)$-alkyl, nitro, $-CF_3$, $-CF_2-CF_3$, $-S(O)_y-R^{14}$, wherein y is 1 or 2, R^{14} is amino, $-(C_1-C_7)$-alkyl, phenyl, which is unsubstituted or mono- to tri- substituted as defined for substituents under 7.1 to 7.9, or $-N(R^{13})_2$,

wherein R^{13} is independently of one another hydrogen atom, $-(C_1-C_7)$-alkyl $-C(O)-(C_1-C_7)$-alkyl, -C(O)-phenyl, -C(O)-O-phenyl, $-C(O)-O-(C_1-C_4)$-alkyl or $-(C_1-C_{10})$-alkyl, wherein alkyl or phenyl are unsubstituted or mono- to tri- substituted independently of one another as defined under 7.1 to 7.9, or

R^{13} together with nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,

$-C(O)-NH-(C_1-C_4)$-alkyl, $-C(O)-O-(C_1-C_4)$-alkyl or $-(C_1-C_{10})$-alkyl, wherein alkyl in each case is unsubstituted or mono- to tri- substituted independently of one another as defined under 7.1 to 7.9,

provided that at least one of R^1, R^2 and R^3 is not a hydrogen atom, and

R^5 is hydrogen atom, $-(C_1-C_{10})$-alkyl, wherein alkyl is unsubstituted or mono- to tri- substituted independently of one another as defined under 7.1 to 7.4,

$-C(O)-R^9$ or $-S(O)_2-R^9$, wherein

R^9 is $-(C_1-C_{10})$-alkyl, $-O-(C_1-C_{10})$-alkyl, wherein alkyl is unsubstituted or mono- to tri- substituted independently of one another as defined under 7.1 to 7.4, or phenyl, which is unsubstituted or mono- to tri- substituted as defined under 7.1 to 7.9, or $-N(R^{13})_2$,

wherein R^{13} is as defined above,

provided that a compound of the formula II, where R^1 is Br and R^2, R^3 and R^5 are each a hydrogen atom is excluded and a compound of the formula II, where R^2 is Br and R^2, R^3 and R^5 are each a hydrogen atom is excluded.

[0010] Most preferred are compounds of formula (II), wherein

R^1, R^2 and R^3 are independently from one another hydrogen atom, halogen, cyano, amino, $-O-(C_1-C_4)$-alkyl, nitro, $-CF_3$ or $N(R^{13})_2$,

wherein R^{13} is independently of one another hydrogen atom, -(C_1-C_7)-alkyl, -C(O)-(C_1-C_7)-alkyl, -C(O)-phenyl or -C(O)-O-(C_1-C_4)-alkyl, wherein alkyl or phenyl are unsubstituted or mono- to tri- substituted independently of one another by halogen or -O-(C_1-C_4)-alkyl, and

R^5 is hydrogen atom, -C(O)-CH_3, methyl, -$S(O)_2$-CH_3, -C(O)-morpholinyl, -CH_2-CH_2-OH or -CH_2-C(O)-NH_2,

provided that no more than two of R^1, R^2, R^3 and R^5 are a hydrogen atom.

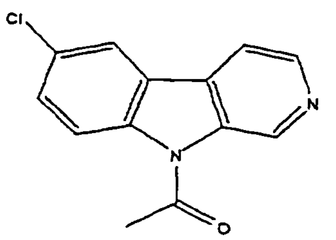
[0011] Most highly preferred are compounds of formula (II), wherein R^1 is bromo, -CF_3 or chloro, R^2 is hydrogen atom or O-(C_1-C_2)-alkyl, R^3 is hydrogen atom, bromo, chloro or -N$(R^{13})_2$,

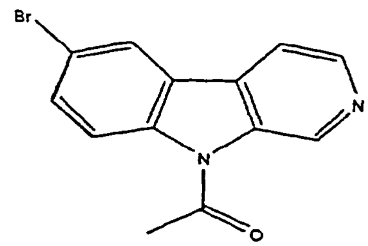
wherein R^{13} is independently of one another hydrogen atom, -C(O)-phenyl, -(C_1-C_7)-alkyl, -C(O)-(C_1-C_4)-alkyl or -C(O)-O-(C_1-C_4)-alkyl, wherein alkyl or phenyl are unsubstituted or mono- to trisubstituted independently of one another by halogen or -O-(C_1-C_2)-alkyl, and

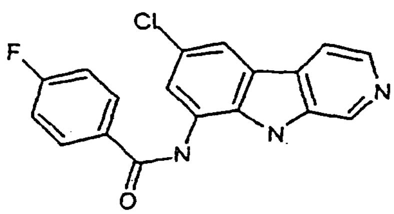
R^5 is hydrogen atom, -C(O)-CH_3, methyl or -$S(O)_2$-CH_3,

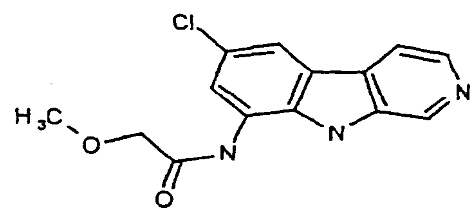
provided that no more than two of R^1, R^2, R^3 and R^5 are a hydrogen atom.

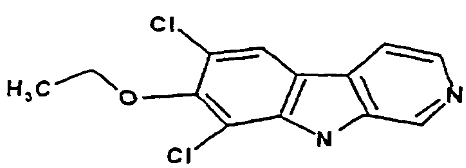
[0012] Specific preferred compounds and all pharmaceutically acceptable salts thereof which are illustrative of the compounds of the invention include the following;

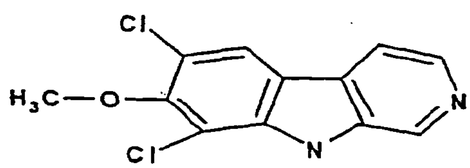












The term "alkyl" by itself or as part on another substituent, unless otherwise stated means a straight or branched chain hydrocarbon radical having 1 to 10 carbon atoms such as methyl, ethyl, n-propyl, isopropyl, n-butyl, tertiary-butyl, hexyl, heptyl, nonyl, octyl decanyl.

The term "alkoxy" by itself or as part on another substituent, unless otherwise stated means -O-alkyl or -O-substituted alkyl.

The term "heterocycle having 5 to 7 ring atoms" represents a radical of a monocyclic saturated system having 5 to 7 ring members, which contains 1, 2 or 3 heteroatoms as ring members. Examples of heteroatoms are N, O and S. Examples of the term heterocycle having 5 to 7 ring atoms are pyrolidine, tetrahydropyridine, piperidine, piperazine, imidazoline, pyrazolidine, morpholine, imidazoline, isoxazolidine, 2-isoxazoline, isothiazolidine, 2-isothiazoline or thiomorpholine.

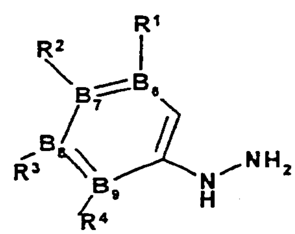
The term "aryl" by itself or as part on another substituent, unless otherwise stated refers to an organic radical derived from an aromatic molecule by removal of one atom; such as phenyl, pyridyl, thiazole, and naphthyl.

The term "substituted alkyl" means an alkyl radical substituted at one or more positions by one or more radicals of the group halogen, nitro, sulfo, amino, substituted amino, carboxyl, alkoxy, -O-aryl, -O-substituted aryl, and hydroxyl. The term "substituted aryl" means an aryl radical substituted at one or more positions by one or more

radicals of the group halogen, alkyl, substituted alkyl, nitro, sulfo, amino, alkoxy, aryl, substituted aryl, or hydroxyl groups, preferred is an aryl radical substituted at 1 to 3 positions by 1 to 3 groups.
The term "substituted amino" refers to $-N(R^{13})_2$ wherein R^{13} is independently of one another hydrogen atom, sulfo, alkyl, aryl, -C(O)-alkyl, C(O)-NH-aryl, -C(O)-O-aryl, -C(O)-O-alkyl, or C(O)-O-aryl, wherein each alkyl or aryl may be independently substituted.
The term "sulfo" refers to $-S(O)y-R^{14}$, wherein R^{14} is an alkyl, aryl, substituted aryl, substituted alkyl, amino, or substituted amino and y is zero, one or two. The term "halogen" is understood as meaning fluorine, chlorine, bromine or iodine.
The term "$-(C_1-C_4)$-alkyl" is understood as meaning hydrocarbon radicals whose carbon chain is linear or branched and contains 1 to 4 carbon atoms.

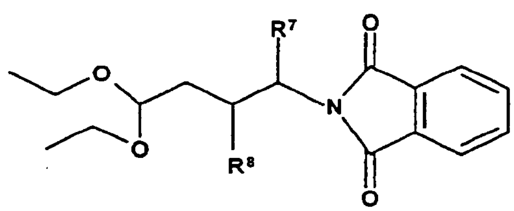
[0013] The invention further relates to a process for the preparation of the compounds of the formula I and/or a stereoisomeric form of the compounds of the formula I and/or of a physiologically tolerable salt of the compounds of the formula I, which comprises

a) reacting a compound of formula III



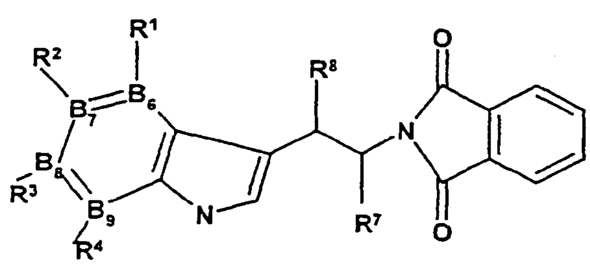
(III)

in which R^1, R^2, R^3, R^4, B_6, B_7, B_8 and B_9 are each as defined in formula I, with a compound of the formula IV,



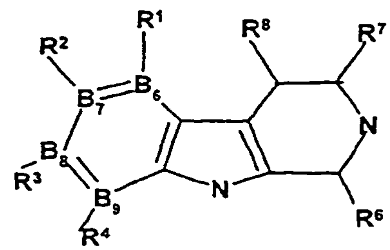
(IV)

in the presence of a acid, converting into a compound of the formula V,



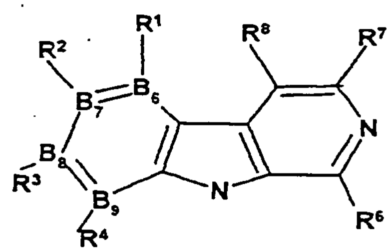
(V)

and is reacted with hydrazine hydrate and later with formaldehyde (R^6 is H) or R^6CHO to give a compound of formula VI



(VI)

and oxidized to give a compound of the formula VII,



(VII)

where R^1 to R^4 and B_6 to B_9 are as defined in formula I and R^5 is hydrogen atom, or

b) a compound of the formula VII is reacted with a compound of the formula VIII

$$Y\text{-}R^5 \qquad \text{(VIII)}$$

where Y is halogen or -OH and R^5 is as defined in formula I, to give a compound of the formula I, or

c) resolving a compound of the formula I, which on account of its chemical structure occurs in enantiomeric forms, prepared by process a) or b) into the pure enantiomers by salt formation with enantiomerically pure acids or bases, chromatography on chiral stationary phases or derivatization by means of chiral enantiomerically pure compounds such as amino acids, separation of the diastereomers thus obtained, and removal of the chiral auxiliary groups, or

d) isolating the compound of the formula I prepared by process a), b) or c) either in free form or, in the case of the presence of acidic or basic groups, converting it into physiologically tolerable salts.

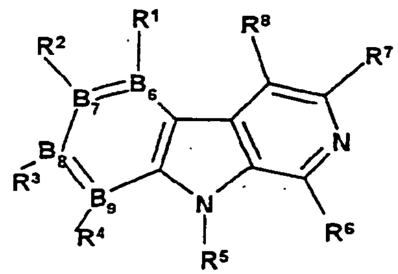
[0014] The preparation of physiologically tolerable salts of compounds of the formula I capable of salt formation, including their stereoisomeric forms, is carried out in a manner known per se. With basic reagents such as hydroxides, carbonates, hydrogencarbonates, alkoxides and also ammonia or organic bases, for example trimethyl- or triethylamine, ethanolamine or triethanolamine or alternatively basic amino acids, for example lysine, ornithine or arginine, the carboxylic acids form stable alkali metal, alkaline earth metal or optionally substituted ammonium salts. If the compounds of the formula I contain basic groups, stable acid addition salts can also be prepared using strong acids. For this, both inorganic and organic acids such as hydrochloric, hydrobromic, sulfuric, phosphoric, methanesulfonic, benzenesulfonic, p-toluenesulfonic, 4-bromobenzenesulfonic, cyclohexylamidosulfonic, trifluoromethylsulfonic, acetic, oxalic, tartaric, succinic or trifluoroacetic acid are suitable.

[0015] The invention also relates to pharmaceuticals which comprise an efficacious amount of at least one compound of the formula I and/or of a physiologically tolerable salt of the compounds of the formula I and/or an optionally stereoisomeric form of the compounds of the formula I, together with a pharmaceutically suitable and physiologically tolerable excipient, additive and/or other active compounds and auxiliaries.

[0016] On account of the pharmacological properties, the compounds according to the invention are suitable for the prophylaxis and therapy of all those disorders in whose course an increased activity of IkB kinase is involved. These include, for example, asthma, rheumatoid arthritis (in the case of inflammation), osteoarthritis, Alzheimer's disease, carcinomatous disorders (potentiation of cytotoxic therapies), cardiac infarct or atherosclerosis.

[0017] The pharmaceuticals according to the invention are in general administered orally or parentally or by rectal, inhale or transdermal administration.

[0018] The invention also relates to the use of the compounds of the formula I



(I)

and/or a stereoisomeric form of the compounds of the formula I and/or a physiologically tolerable salt of the compounds of the formula I,
where B_6, B_7, B_8 and B_9 are independently selected from the group consisting of carbon atom and nitrogen atom and where B_6, B_7, B_8 and B_9 together are no more than two nitrogen atoms at the same time;
where the substituents R^1, R^2, R^3, R^4 and R^8 independently of one another are

1. hydrogen atom,
2. halogen,
3. -OH,
4. -CN,
5. sulfo,
6. $-NO_2$,
7. $-NH_2$,
8. alkoxy,
9. substituted amino,
10. -COOH,
11. $-O-R^{10}$, wherein R^{10} is alkyl, substituted alkyl or aryl,
12. $-C(O)-R^{12}$, wherein R^{12} is alkyl, substituted alkyl or aryl,
13. $-C(O)-O-R^{12}$, wherein R^{12} is as defined above,
14. aryl,
15. -O-aryl,
16. substituted aryl,
17. -O-substituted aryl,
18. alkyl,
19. substituted alkyl,
20. $-CF_3$ or
21. $-CF_2-CF_3$,

provided that at least one of R^1, R^2, R^3, R^4 and R^8 is not a hydrogen atom,

R^5 is

1. hydrogen atom,
2. alkyl,
3. alkyl radical, substituted at one or more positions by one or more of the radicals, halogen, amino or hydroxyl,
4. $-C(O)-R^9$ or
5. $-S(O)_2-R^9$, in which
   R^9 is

   a) alkyl,
   b) alkyl radical, substituted at one or more positions by one or more of the radicals, halogen, amino or hydroxyl,

c) aryl,
d) aryl radical, substituted at one or more positions by one or more of the radicals, halogen, amino, or hydroxyl,
e) $-NH_2$,
f) alkoxy or
g) substituted amino, and

R6 and R7 independently of one another are

1. hydrogen atom,
2. halogen,
3. -OH,
4. methyl,
5. $-O-(C_1-C_{10})$-alkyl, wherein alkyl is unsubstituted or mono- to trisubstituted independently of one another by

    5.1 aryl,
    5.2 halogen,
    5.3 $-NO_2$,
    5.4 sulfo,
    5.5 -COOH,
    5.6 $-NH_2$,
    5.7 $-O-(C_1-C_4)$-alkyl or
    5.8 -OH, or

6. $N(R^{13})_2$, wherein R^{13} is independently of one another hydrogen atom, aryl, $-C(O)-(C_1-C_4)$-alkyl or substituted aryl or alkyl, wherein alkyl is unsubstituted or mono- to tri- substituted independently of one another as defined under 5.1 to 5.8, or R^{13} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms.

[0019] Preferred is the use of the compounds of formula I, wherein B_6, B_7, B_8, and B_9 are each a carbon atom, R^1, R^2, R^3, R^4 and R^8 independently of one another are

1. hydrogen atom,
2. halogen,
3. -CN,
4. -COOH,
5. $-NO_2$,
6. $-NH_2$,
7. $-O-(C_1-C_{10})$-alkyl, wherein alkyl is mono- to penta- substituted independently of one another by

    7.1 phenyl, which is unsubstituted or mono- to pentasubstituted by halogen or $-O-(C_1-C_4)$-alkyl,
    7.2 halogen,
    7.3 $-NH_2$,
    7.4 -OH,
    7.5 -COOH,
    7.6 $-NO_2$,
    7.7 $-S(O)_y-R^{14}$, wherein y is zero, 1 or 2, R^{14} is $-(C_1-C_{10})$-alkyl, phenyl, which is unsubstituted or mono- to pentasubstituted as defined for substituents under 7.1 to 7.9, amino or $-N(R^{13})_2$, wherein R^{13} is independently of one another hydrogen atom, phenyl, $-(C_1-C_{10})$-alkyl, $-C(O)-(C_1-C_7)$-alkyl, -C(O)-phenyl, $-C(O)-NH-(C_1-C_7)$-alkyl, -C(O)-O-phenyl, -C(O)-NH-phenyl, $-C(O)-O-(C_1-C_7)$-alkyl, $-S(O)_y-R^{14}$, wherein R^{14} and y are as defined above,
    and wherein alkyl or phenyl in each case are unsubstituted or mono- to penta- substituted independently of one another as defined under 7.1 to 7.9 above, or
    R^{13} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,
    7.8 $-O-(C_1-C_{10})$-alkyl or
    7.9 -O-phenyl,

8. $-N(R^{13})_2$, wherein R^{13} is as defined in 7.7 above,

9. $-S(O)y-R^{14}$, wherein R^{14} and y are as defined in 7.7 above,
10. $-C(O)-R^{12}$, wherein R^{12} is phenyl or $-(C_1-C_7)$-alkyl, wherein alkyl or phenyl are unsubstituted or mono- to pentasubstituted independently of one another as defined under 7.1 to 7.9 above,
11. $-C(O)-O-R^{12}$, wherein R^{12} is as defined under 10. above,
12. $-(C_1-C_{10})$-alkyl, wherein alkyl is unsubstituted or mono- to pentasubstituted independently of one another as defined under 7.1 to 7.9 above,
13. $-CF_3$ or
14. $-CF_2-CF_3$,

provided that at least one of R^1, R^2, R^3, R^4 and R^8 is not a hydrogen atom,
R^5 is

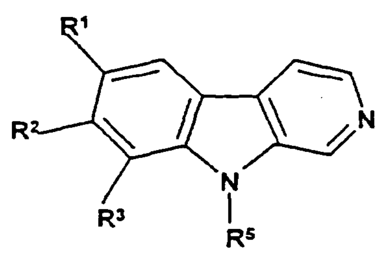
1. hydrogen atom,
2. $-(C_1-C_{10})$-alkyl, wherein alkyl is unsubstituted or mono- to pentasubstituted independently of one another as defined under 7.1 to 7.4 above,
3. $-C(O)-R^9$, wherein R^9 is
$-NH_2$, $-(C_1-C_{10})$-alkyl, wherein alkyl is unsubstituted or mono- to penta- substituted independently of one another as defined under 7.1 to 7.4, or $-N(R^{13})_2$, wherein R^{13} is as defined in 7.7 above, or
4. $-S(O)_2-R^9$, wherein R^9 is as defined in 3 above, and

R^6 and R^7 independently of one another are hydrogen atom or methyl.

[0020] More preferred is the use of compounds of formula I for the production of pharmaceuticals for the prophylaxis and therapy of disorders in whose course an increased activity of I_kB kinase is involved, wherein

B_6, B_7, B_8, and B_9 are each a carbon atom,
R^1, R^2, R^3 and R^4 independently of one another are hydrogen atom, halogen, cyano, nitro, amino, $-O-(C_1-C_7)$-alkyl, phenyl, -O-phenyl, $-CF_3$, $-CF_2-CF_3$, $-N(R^{13})_2$,
wherein R^{13} is independently of one another hydrogen atom, $-(C_1-C_7)$-alkyl, phenyl, -C(O)-phenyl, -C(O)-NH-phenyl, -C(O)-O-phenyl, $-C(O)-O-(C_1-C_4)$-alkyl, $-C(O)-(C_1-C_7)$-alkyl or-(C_1-C_{10})-alkyl, wherein alkyl or phenyl are unsubstituted or mono- to trisubstituted independently of one another as defined under 7.1 to 7.9, or R^{13} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,
$S(O)_y-R^{14}$, wherein y is zero, 1 or 2, and R^{14} is $-(C_1-C_{10})$-alkyl, phenyl, which is unsubstituted or mono- to penta- substituted as defined for substituents under 7.1 to 7.9, amino or $-N(R^{13})_2$, wherein R^{13} is as defined above,
wherein alkyl is unsubstituted or mono- to tri- substituted independently of one another as defined under 7.1 to 7.9, or $-C(O)-O-R^{12}$, wherein R^{12} is as defined above,
R^6, R^7 and R^8 independently of one another are hydrogen atom, methyl, amino, $-N(R^{13})_2$, wherein R^{13} is as defined above, provided that at least one of R^1, R^2, R^3, R^4 and R^8 is not a hydrogen atom, and
R^5 is as defined above.

[0021] Even more preferred is the use of compounds of formula II



(II)

and/or a stereoisomeric form of the compounds of the formula II and/or a physiologically tolerable salt of the compounds of the formula II, for the production of pharmaceuticals for the prophylaxis and therapy of disorders in whose course an increased activity of I_kB kinase is involved, wherein;
R^1, R^2 and R^3 are independently from one another hydrogen atom, halogen, cyano, amino, $-O-(C_1-C_4)$-alkyl, nitro, $-CF_3$, $-CF_2-CF_3$, $-S(O)_y-R^{14}$, wherein y is 1 or 2,
R^{14} is amino, $-(C_1-C_7)$-alkyl, phenyl, which is unsubstituted or mono- to tri- substituted as defined for sub-

stituents under 7.1 to 7.9, or $-N(R^{13})_2$,

wherein R^{13} is independently of one another hydrogen atom, $-(C_1-C_7)$-alkyl $-C(O)-(C_1-C_7)$-alkyl, -C(O)-phenyl, -C(O)-O-phenyl, $-C(O)-O-(C_1-C_4)$-alkyl or $-(C_1-C_{10})$-alkyl, wherein alkyl or phenyl are unsubstituted or mono- to trisubstituted independently of one another as defined under 7.1 to 7.9, or

R^{13} together with nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,

$-C(O)-NH-(C_1-C_4)$-alkyl, $-C(O)-O-(C_1-C_4)$-alkyl or $-(C_1-C_{10})$-alkyl, wherein alkyl in each case is unsubstituted or mono- to trisubstituted independently of one another as defined under 7.1 to 7.9,

provided that at least one of R^1, R^2 and R^3 is not a hydrogen atom, and

R^5 is hydrogen atom, $-(C_1-C_{10})$-alkyl,

wherein alkyl is unsubstituted or mono- to tri- substituted independently of one another as defined under 7.1 to 7.4, $-C(O)-R^9$ or $-S(O)_2-R^9$, wherein

R^9 is $-(C_1-C_{10})$-alkyl, $-O-(C_1-C_{10})$-alkyl,

wherein alkyl is unsubstituted or mono- to tri- substituted independently of one another as defined under 7.1 to 7.4, phenyl, which is unsubstituted or mono- to tri- substituted as defined under 7.1 to 7.9, or $-N(R^{13})_2$,

wherein R^{13} is as defined above.

[0022] Most preferred is the use of the compounds of formula II for the production of pharmaceuticals for the prophylaxis and therapy of disorders in whose course an increased activity of I_kB kinase is involved, wherein

R^1, R^2 and R^3 are independently from one another hydrogen atom, halogen, cyano, amino, $-O-(C_1-C_4)$-alkyl, nitro, $-CF_3$ or $N(R^{13})_2$,

wherein R^{13} is independently of one another hydrogen atom, $-(C_1-C_7)$-alkyl, $-C(O)-(C_1-C_7)$-alkyl, -C(O)-phenyl or $-C(O)-O-(C_1-C_4)$-alkyl, wherein alkyl or phenyl are unsubstituted or mono- to tri- substituted independently of one another by halogen or $-O-(C_1-C_4)$-alkyl, and

R^5 is hydrogen atom, $-C(O)-CH_3$, methyl, $-S(O)_2-CH_3$, -C(O)-morpholinyl, $-CH_2-CH_2-OH$ or $-CH_2-C(O)-NH_2$,

provided that no more than two of R^1, R^2, R^3 and R^5 are a hydrogen atom.

[0023] Most highly preferred is the use of the compounds of formula II for the production of pharmaceuticals for the prophylaxis and therapy of disorders in whose course an increased activity of IkB kinase is involved, wherein R^1 is bromo, $-CF_3$ or chloro, R^2 is hydrogen atom or $O-(C_1-C_2)$-alkyl, R^3 is hydrogen atom, bromo, chloro or $-N(R^{13})_2$, wherein R^{13} is independently of one another hydrogen atom, -C(O)-phenyl, $-(C_1-C_7)$-alkyl, $-C(O)-(C_1-C_4)$-alkyl or $-C(O)-O-(C_1-C_4)$-alkyl, wherein alkyl or phenyl are unsubstituted or mono- to tri- substituted independently of one another by halogen or $-O-(C_1-C_2)$-alkyl, and

R^5 is hydrogen atom, $-C(O)-CH_3$, methyl or $-S(O)_2-CH_3$, provided that no more than two of R^1, R^2, R^3 and R^5 are a hydrogen atom.

[0024] Specific preferred is the use of the compounds of formula II for the production of pharmaceuticals for the prophylaxis and therapy of disorders in whose course an increased activity of IkB kinase is involved, wherein

R^1 is chloro, R^2 and R^3 are each hydrogen atom, and R^5 is $-C(O)-CH_3$, or

R^1 is bromo, R^2 and R^3 are each hydrogen atom, and R^5 is $-C(O)-CH_3$, or

R^1 is chloro, R^3 is $-N-C(O)-CH_2-O-CH_3$ and R^2 and R^5 are each hydrogen atom, or R^1 is chloro, R^3 is -N-C(O)-para-fluoro-phenyl and R^2 and R^5 are each hydrogen atom, or R^1 and R^3 are each chloro, R^2 is $-C(O)-CH_3$ and R^5 is hydrogen atom, or

R^1 and R^3 are each chloro, R^5 is hydrogen atom and R^2 is $-C(O)-CH_2-CH_3$.

[0025] Disorders in whose course an increased activity of IkB kinase is involved include, for example, asthma, osteoarthritis, rheumatoid arthritis (in the case of inflammation), Alzheimer's disease, carcinomatous disorders (potentiation of cytotoxic therapies) and cardiac infarct.

[0026] The invention also relates to a process for the production of a pharmaceutical, which comprises bringing at least one compound of the formula I into a suitable administration form using a pharmaceutically suitable and physiologically tolerable excipient and, if appropriate, further suitable active compounds, additives or auxiliaries.

[0027] Suitable solid or pharmaceutical preparation forms are, for example, granules, powders, coated tablets, tablets, (micro)capsules, suppositories, syrups, juices, suspensions, emulsions, drops or injectable solutions, and preparations having protracted release of active compound, in whose preparation customary auxiliaries, such as excipients, disintegrants, binders, coating agents, swelling agents, glidants or lubricants, flavourings, sweeteners and solubilizers are used. Frequently used auxiliaries which may be mentioned are magnesium carbonate, titanium dioxide, lactose, mannitol and other sugars, talc, lactoprotein, gelatin, starch, cellulose and its derivatives, animal and vegetable oils such as cod liver oil, sunflower, groundnut or sesame oil, polyethylene glycol and solvents such as, for example, sterile water and mono-or polyhydric alcohols such as glycerol.

[0028] The pharmaceutical preparations are preferably produced and administered in dose units, each unit containing as active constituent a certain dose of the compound of the formula I according to the invention. In the case of solid

dose units such as tablets, capsules, coated tablets or suppositories, this dose can be up to approximately 1000 mg, preferably from approximately 50 mg to 300 mg and in the case of injection solutions in ampoule form up to approximately 300 mg, preferably from approximately 10 mg to 100 mg.

[0029] For the treatment of an adult patient weighing approximately 70 kg, depending on the efficacy of the compound according to formula I, daily doses of approximately 20 mg to 1000 mg of active compound, preferably from approximately 100 mg to 500 mg, are indicated. Under certain circumstances, however, even higher or lower daily doses may be appropriate. The administration of the daily dose can be carried out both by single administration in the form of an individual dose unit or else of a number of smaller dose units and by multiple administration of subdivided doses at specific intervals.

[0030] As a rule, final products are determined by mass-spectroscopic methods (FAB-, ESI-MS). Temperatures are given in degrees Celsius, RT means room temperature (22 °C to 26 °C). Abbreviations used are either explained or correspond to the customary conventions.

Example 1, 7-bromo-β-carboline

[0031] A solution of norharmane (600 mg, 3.57 mmol) in tetrahydrofuran (THF; 50 ml) was treated with bromine (0.40 ml, 7.80 mmol) at RT while stirring. After stirring for 18 h at RT, the reaction was concentrated under reduced pressure and the resulting residue was sonicated in 10% aqueous Na_2CO_3 (100 ml). The product was filtered and washed with water to give 905 mg of crude product. The crude product was crystallized from xylenes to provide in two crops 580 mg of 7-bromo-β-carboline.

Example 2, 1-acetyl-7-bromo- β -carboline

[0032] A solution of Example 1 (25 mg, 0.1 mmol) in dimetylformamide (DMF; 2 ml) was treated with 0.10 ml of 1M aqueous NaOH (0.10 mmol). After stirring at RT for 30 minutes, acetic anhydride (0.010 ml, 0.095 mmol) was added and reaction stirred 18 h at RT. The reaction was partitioned in EtOAc and 5% citric acid and the organic layer washed with water, dried (brine; MgSO4), and concentrated to give 23 mg of crude product. The crude product was chromatographed (7:3 hexane-acetone) on silica gel to give 10 mg of 1-acetyl-7-bromo-β-carboline.

Example 3, 7-fluoro- β -carboline

[0033] A mixture of 5-fluorotryptamine hydrochloride (200 mg, 0.93 mmol) in EtOAc (4 ml) and water (2 ml) was treated with glyoxalic acid hydrate (90 mg, 0.98 mmol). The pH of the aqueous layer was adjusted to 5 (with 5% $NaHCO_3$ then 1M HCl) and the mixture stirred vigorously at RT for 18 h. The mixture was then diluted with hexane (4 ml) and the product filtered and washed with water and (1:1) hexane-ethyl acetate.

[0034] The crude product from above in 6N HCl (3 ml) was treated 3 times with concentrated HCl (0.050 ml) every 15 min while refluxing. After refluxing for a total of 45 min, the reaction was concentrated to give a residue. The above residue was slurred in xylenes with triethylamine (0.40 ml, 2.9 mmol) and 10% Pd/C (200 mg). The mixture was refluxed for 1 h and then filtered hot through celite. The filtrate was concentrated and the residue chromatographed (5:95 methanol-chloroform) on silica gel to give 25 mg of 7-fluoro-β-carboline.

Example 4, 7-isopropyl- β -carboline hydrochloride

[0035] A mixture of 4-isopropylphenylhydrazine hydrochloride (660 mg, 3.55 mmol) and 4-phthalimidobutanal diethyl acetal (1.15 g, 3.95 mmol) in Ethanol (EtOH; 30 ml) was heated at 60 °C to 65 °C for 1 h with water (0.050 ml). The mixture was then treated with concentrated HCl (0.50 ml) and refluxed for 14 h. After concentrating the reaction, the residue was partioned in methylene chloride and saturated aqueous $NaHCO_3$. The aqueous solution was extracted with methylene chloride (3 times) and the combined organic solutions were dried ($MgSO_4$) and concentrated to give after chromatography (4:1 hexane-ethyl acetate) on silica gel 146 mg of product.

[0036] The above product was treated with hydrazine hydrate (1 ml) in EtOH (4 ml) and water (1 ml) and stirred at RT overnight. After concentrating the reaction to an aqueous mixture, the product was extracted with methylene chloride (3 times). The combined organic solution was dried ($MgSO_4$) and concentrated. The residue was redissolved in methylene chloride and treated with 1M HCl in ether. The precipitate was collected and washed with ether and hexane and dried to provide 102 mg of 6-isopropyltryptamine hydrochloride salt. This tryptamine obtained above was transformed into 7-Isopropyl- β -carboline according to the procedure used in example 3. The hydrochloride salt was obtained by treating a solution of 7-Isopropyl-β-carboline in methylene chloride with 1M HCl in ether and concentrating. The residue was triturated with (1:1) methylene chloride-hexane to give 15 mg of 7-isopropyl-β-carboline hydrochloride.

Example 5, 7-cyano- β -carboline

[0037] A dark solution of example 1 (190 mg, 0.62 mmol) and CuCN (110 mg, 1.22 mmol) in N-methyl 2-pyrrolidone (1.5 ml) was heated in a sealed reaction tube at 200 °C for 48 h. The mixture was filtered and the filtrate was diluted with water (50 ml). A brown solid that precipitated was filtered, washed with water, saturated aqueous $NaHCO_3$, and then methanol. This material was dissolved in DMSO and diluted with aqueous HCl. This homogeneous dark solution was decolorized with charcoal, filtered and concentrated to give a concentrated solution in DMSO. This DMSO solution was partitioned in (1:1) EtOAc-THF and saturated aqueous $NaHCO_3$. The organic solution was dried ($MgSO_4$) and concentrate to give 8 mg of 7-cyano- β -carboline.

Example 6, 7-nitro-β- carboline hydrochloride

[0038] Norharmane (100 mg, 0.60 mmol) was treated with concentrated nitric acid (1.0 ml) and the resulting suspension was heated to 65 °C until the mixture became homogeneous (3 to 4 min). The solution was carefully poured into water (20 ml), and the precipitate filtered and washed with water then methanol. The solid was suspended in saturated aqueous $NaHCO_3$ and stirred vigorously before filtering and washing with water. The solid was taken up in hot methanol and this solution treated with 1M HCl in ether (5 ml). The solution was concentrated and the residue triturated with ether to provide 58 mg of a 7:3 mixture of 7-nitro- β -carboline hydrochloride and 9-nitro- β-carboline hydrochloride.

Example 7, 7-carboxy- β - carboline trifluoroacetat

[0039] Crude product from example 5 (from 210 mg of example 1, 0.85 mmol) was treated with 6 M HCl in a sealed reaction tube for 15 h at 110 °C. The reaction was evaporated to give a concentrated solution of product in N-methyl 2-pyrrolidone. A portion (half) was purified by preparative HPLC using a C_{18}-packed column and eluting with a gradient (5:95 to 50:50) of water-acetonitril (with 0.1% trifluoracetic acid). The pure fractions were combined and lyophilized to provide 11 mg of 7-carboxy- β -carboline trifluoroacetate.

Example 8, 7,9-dibromo- β - carboline hydrochloride

[0040] A solution of the product from example 1 (140 mg, 0.58 mmol) in THF (2 ml) was treated with bromine (0.50 ml). After 10 min at RT, the reaction was diluted with chloroform and the product was filtered. The filtered product was taken up in methanol and treated with 1M HCl in ether and concentrated. The residue was triturated with ether to provide 160 mg of 7,9-dibromo- β-carboline hydrochloride.

Example 9, 7,9-dichloro- β - carboline

[0041] To a suspension of norharmane (84 mg, 0.50 mmol) in water (3 ml) at RT was added 1M aqueous HCl (1.1 ml, 1.1 mmol). To this homogenous solution was added N-chlorosuccinimide (747 mg, 5.58 mmol) portionwise and the resulting solution was stirred at 60 °C to 70 °C for 3h. The reaction was partitioned in EtOAc and saturated aqueous $NaHCO_3$ and the organic layer was dried (brine; $MgSO_4$) and then concentrated. The residue was chromatographed (2:3 THF-hexane) on silica gel to give 24 mg of 7,9-dichloro- β -carboline after triturating with (1:1) methylene chloride-hexane, then with hexane.

Example 10, 1-acetyl-7-bromo- β - carboline

[0042] To a suspension of NaH (95%, 14 mg, 0.60 mmol) in DMF (1.0 ml) at 5 °C to 10 °C was added the product from example 1 (74 mg, 0.30 mmol). The resulting mixture was stirred for 15 min at 5 °C to 10 °C before adding methanesulfonylchloride (0.030 ml, 0.38 mmol). The reaction was allowed to warm to RT and stirred for 2 h before partitioning into saturated aqueous $NaHCO_3$ and EtOAc. After stirring the mixture overnight, the organic layer was washed with water, dried (brine; $MgSO_4$), and concentrated. The residue was purified by chromatography (1:1 hexane-ethyl acetate) on silica gel to give 23 mg of 1-acetyl-7-bromo- β-carboline.

Example 11, 7-bromo-1-methyl- β - carboline

[0043] To a suspension of NaH (95%, 6 mg, 0.24 mmol) in DMF (2.0 ml) at 5 °C to 10 °C was added the product from example 1 (50 mg, 0.20 mmol). The resulting mixture was stirred for 15 min at 5 °C to 10 °C before adding methyl-iodide (0.030 ml, 0.20 mmol) at 0 °C to 5 °C. The reaction stirred for 12 h at 0 °C to 5 °C before partitioning into water

and EtOAc. The organic layer was washed with water, dried (brine; $MgSO_4$), and concentrated. The residue was purified by chromatography (gradient, 1:3 hexane-ethyl acetate to ethyl acetate) on silica gel to give 10 mg of 7-bromo-1-metyhl-β -carboline.

Example 12, 7-chloro- β - carboline

[0044] To a solution of norharmane (2.0 g, 11.9 mmol) in water (89 ml) and 1 M aqueous HCl (29.8 ml, 29.8 mmol) was added N-chlorosuccinimide (3.17 g, 23.8 mmol) portionwise. The resulting solution was stirred at RT for 6 h, and then at 0 °C to 5 °C for 12 h. The reaction was diluted with water (100 ml) and basified cautiously with solid K_2CO_3 (4.3 g). After stirring at RT for 1 h, the product was collected and washed with water. The crude product was refluxed in chloroform for 1 h and filtered after cooling to 15 °C to provide 2.05 g of 7-chloro- β -carboline.

Example 13, 1-acetyl-7-chloro- β - carboline

[0045] To a solution of the product from example 12 (104 mg, 0.50 mmol) in DMF (2.0 ml) at 3 °C to 5 °C was added NaH (95%, 15 mg, 0.625 mmol). The resulting mixture was stirred for 15 min before adding acetic anhydride (0.083 ml, 0.875 mmol). The reaction was allowed to warm to RT and stirred for 3 h before pouring into with water (25 ml). The slurry was stirred for 12 h, and the product collected to give after chromatography (1:3 hexane-ethyl acetate) on silica gel 82 mg of 1-acetyl-7-chloro- β -carboline.

Example 14, 7-chloro-9-nitro- β - carboline

[0046] A mixture of the product from example 12 (500 mg, 2.48 mmol) in concentrated nitric acid (20 ml) was stirred at RT for 22 h. The reaction mixture was carefully poured into cold (3 °C to 5 °C) water (50 ml), and after stirring for 2 h the precipitate was collected. The solid was suspended in saturated aqueous $NaHCO_3$ (50 ml) and stirred at RT for 12 h. The product was filtered and washed with water to provide 550 mg of 7-chloro-9-nitro- β -carboline

Example 15, 9-amino-7-chloro- β - carboline

[0047] To a suspension of the product from example 14 (548 mg, 2.22 mmol) in EtOH (14 ml) at 65 °C to 70 °C was added tin chloride dihydrate (2.5 g, 11.1 mmol).

[0048] Thereafter, 6M aqueous HCl (14 ml) was added dropwise. The mixture was stirred at 70 °C to 80 °C for 3.5 h and then partitioned slowly into saturated aqueous $NaHCO_3$ (150 ml) and EtOAc (100 ml). The aqueous phase was extracted (2 times) and the combined organic solutions dried (brine; $NaSO_4$) and concentrated to give 484 mg of 9-amino-7-chloro- β -carboline.

Example 16, 9-amino-7-chloro- β - carboline trifuoroacetate

[0049] To a solution of the product from example 15 (35 mg, 0.16 mmol) in pyridine (0.80 ml) was added acetic anhydride (0.018 ml, 0.19 mmol). The resulting mixture was allowed to stand at RT for 12 h before pouring into water (15 ml). The crude product was filtered and purified by preparative HPLC using a C_{18}-packed column and eluting with a gradient (5:95 to 60:40) of water-acetonitril (with 0.1% trifluoracetic acid). The pure fractions were combined and lyophilized to provide 18 mg of 9-amino-7-chloro- β -carboline trifluoroacetate.

Example 17, 7-bromo-1-carbonyl-(4'-morpholine)- β - carboline

[0050] A solution of the product from example 1 (125 mg, 0.51 mmol) in DMF (2 ml) was treated with 0.55 ml of 1M aqueous NaOH (0.55 mmol). After stirring at RT for 30 minutes, 4-morpholinecarbonyl chloride (0.060 ml, 0.51 mmol) was added and reaction stirred 18 h at RT. The reaction was partitioned in EtOAc and 5% citric acid and the organic layer washed with water, dried (brine; $MgSO_4$), and concentrated. The residue was chromatographed (7:3 hexane-acetone) on silica gel to give 105 mg of 7-bromo-1-carbonyl-(4'-morpholino)- β -carboline.

Example 18, 1-(2'-ethylacetate)-7-chloro- β - carboline

[0051] To a suspension of NaH (95%, 28 mg, 1.15 mmol) in DMF (1.0 ml) at 5 °C to 10 °C was added the product from example 12 (202 mg, 1.0 mmol) in DMF (3 ml). The resulting mixture was stirred for 30 min at 5 °C to 10 °C before adding ethyl bromoacetate (0.116 ml, 1.05 mmol). The reaction was allowed to be stirred for 1.5 h and then the reaction was diluted with saturated aqueous $NaHCO_3$ (30 ml). The product was extracted with EtOAc (30 ml; 2 times each

15ml), and the combined organic extracts were dried (brine; $MgSO_4$) then concentrated. The residue was purified by chromatography (1:3 hexane-ethyl acetate) on silica gel to give 270 mg of 1-(2'ethylacetate)-7-chloro- β-carboline.

Example 19, 1-(2'-ethanoyl)-7-chloro- β - carboline

[0052] To a solution of the product from example 18 (50 mg, 0.17 mmol) in THF (1.7 ml) at 5 °C to 10 °C was added 1M LAH in THF (0.17 ml, 0.17 mmol). The resulting mixture was stirred for 2 h at 5 °C to 10 °C before adding EtOAc (0.10 ml). The mixture was subsequently diluted with EtOAc (5 ml) and slowly treated with saturated aqueous $NaHCO_3$ (5 ml). After diluting with water (10 ml) and brine (10 ml) the mixture was extracted with EtOAc. The organic solution was dried (brine; $MgSO_4$) then concentrated to give 42 mg of 1-(2'ethanol)-7-chloro- β -carboline.

Example 20, 1-(2'-acetyl)-7-chloro- β - carboline

[0053] To a solution of the product from example 18 (107 mg, 0.37 mmol) in MeOH (3.7 ml) at RT was added water (3.7 ml) followed by treatment with 1M aqueous NaOH (0.41 ml, 0.41 mmol). The resulting mixture was stirred for 2 h and the volatile removed under reduced pressure. The mixture was subsequently diluted with water (5 ml) and the pH adjusted to 5 to 6. The precipitate was filtered and washed with water to give 96 mg of 1-(2'-acetyl)-7-chloro- β -carboline.

Example 21, 8-methoxy- β - carboline

[0054] Prepared from 6-methoxytryptamine using the procedure as in example 3.

Example 22, see table 1 for structure

[0055] To a solution of the product from example 20 (59 mg, 0.23 mmol) in DMF (2.8 ml) at RT was added p-nitrophenol (40 mg, 0.29 mmol) followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (48 mg, 0.25 mmol). The resulting mixture was stirred for 1.5 h at RT and then ammonium bicarbonate (55 mg, 0.69 mmol) was added. The reaction was stirred for 18 h at RT and then poured into water (20 ml). The aqueous mixture was basified to pH of about 10 with K_2CO_3. The precipitate was filtered and washed with water to give 47 mg of the title compound.

Example 23, 8-hydroxy-2-methyl- β - carboline

[0056] A solution of harmine (616 mg, 2.9 mmol) in dichloroethane (20 ml) was treated with 2.0 ml of 1M BBr_3 (4 mmol) in dichloroethane. The reaction was stirred at 60 °C for 48 h and then cooled to 0 °C before quenching with MeOH (5 ml). The reaction was concentrated and the residue triturated with methanol to give 413 mg of 8-hydroxy-2-methyl- β -carboline .

Example 24, 6,8-dibromo-7-methoxy- β - carboline

[0057] A solution of the product from example 30 (90 mg, 0.45 mmol) in acetic acid (8 ml) was treated with bromine (0.025 ml, 0.48 mmol). The reaction was stirred at RT for 18 h and then concentrated. The residue was partitioned in EtOAc and aqueous $NaHCO_3$. The organic layer was dried (brine; $MgSO_4$) and concentrated. The residue was purified by chromatography (5:4 hexane-acetone) on silica gel to give 3 mg of 6,8-dibromo-7-methoxy- β -carboline.

Example 25, see table 1 for structure

[0058] A solution of the product from example 23 (60 mg, 0.30 mmol) in DMF (3 ml) was treated with K_2CO_3 (100 mg) and t-butyl bromoacetate (0,040 ml, 0.27 mmol). After stirring at RT for 18 h, the reaction was partitioned in EtOAc and water. The organic layer was dried (brine; $MgSO_4$) and then concentrated. The residue was chromatographed (1:1 hexane-EtOAc) on silica gel to give 20 mg of the title compound.

Example 26, see table for structure

[0059] A solution of the product from example 23 (50 mg, 0.25 mmol) in DMF (3 ml) was treated with K_2CO_3 (100 mg) and benzyl bromide (0,030 ml, 0.25 mmol). After stirring at RT for 18 h, the reaction was partitioned in EtOAc and water. The organic layer was dried (brine; $MgSO_4$) and then concentrated. The residue was chromatographed (1:1 hexane-EtOAc) on silica gel to give 12 mg of the title compound.

Example 27, 7-ethoxy-2-methyl- β - carboline

[0060] A solution of the product from example 23 (60 mg, 0.30 mmol) in DMF (3 ml) was treated with K_2CO_3 (100 mg) and ethyl iodide (0,029 ml, 0.36 mmol).

[0061] After stirring at RT for 18 h, the reaction was partitioned in EtOAc and water. The organic layer was dried (brine; $MgSO_4$) and then concentrated. The residue was chromatographed (1:1 hexane-acetone) on silica gel to give 20 mg of 7-ethoxy-2-methyl- β-carboline.

Example 28, 7-bromo-2-methyl- β - carboline

[0062] Prepared from harmane using the same procedure as in example 1.

Example 29, see table 1 for structure

[0063] A solution of the product from example 23 (60 mg, 0.30 mmol) in DMF (3 ml) was treated with K_2CO_3 (100 mg) and acetic anhydride (0,034 ml, 0.36 mmol). After stirring at RT for 18 h, the reaction was partitioned in EtOAc and water. The organic layer was dried (brine; $MgSO_4$) and then concentrated. The residue was chromatographed (1: 1 hexane-acetone) on silica gel to give 18 mg of the title compound.

Example 30, 7-methoxy- β - carboline

[0064] Prepared from 5-methoxytryptamine using the procedure in example 3.

Example 31, 8-fluoro- β - carboline

[0065] Prepared from 6-fluorotryptamine using the same procedure as in example 3.

Example 32, 7-bromo-2-methyl-8-methoxy- β - carboline

[0066] Prepared from harmine using the same procedure as in example 1.

Example 33, 7-hydroxy- β - carboline

[0067] Prepared from the product of example 30 using the procedure in example 23.

Example 34, 7-chloro-8-fluoro- β - carboline

[0068] Prepared from the product of example 31 using the procedure in example 12.

Example 35, 7-methoxy-1-methyl- β - carboline

[0069] Prepared from the product of example 30 using the procedure in example 11.

Example 36 9-chloro-8-methoxy-β-carboline trifluoroacetate and Example 37 7,9-dichloro-8- methoxy-β-carboline trifluoroacetate

[0070] A solution of the product from example 21 (195 mg, 1.0 mmol) in 1 M HCl (3 ml) was treated with N-chlorosuccinimide (270 mg, 2 mmol) portionwise and the resulting solution was stirred at 60 °C to 70 °C for 3h. The reaction was evaporated and the crude product purified by preparative HPLC using a C_{18}-packed column and eluting with a gradient (5:95 to 50:50) of water-acetonitril (with 0.1% trifluoroacetic acid). The pure fractions of each product were combined and lyophilized to provide 78 mg of 9-chloro-8-methoxy-β-carboline trifluoroacetate and 51 mg of 7,9-dichloro-8- methoxy-β-carboline trifluoroacetate.

Example 38 7,9-dichloro-8-hydroxy-β-carboline

[0071] A mixture of the product of example 37 (590 mg, 2.21 mmol) in methylene chloride (25 ml) at 35 °C was treated with a solution of BBr_3 in methylene chloride (1M, 6 ml, 6 mmol). After refluxing for 3h, the reaction was quenched with methanol (5 ml) and then concentrated. The residue was slurred in 60% $NaHCO_3$ solution, the product filtered

and washed with water to give 500 mg of 7,9-dichloro-8-hydroxy-β-carboline.

Example 39 7,9-dichloro-8-ethoxy-β-carboline

[0072] A mixture of the product of example 38 (35 mg, 0.14 mmol), K_2CO_3 (100 mg), and ethyl iodide (0.014 ml, 0.17 mmol) in acetone (5 ml) was stirred in a closed reaction tube at RT for 3 days. After concentrating the reaction, the residue was partitioned in ethyl acetate and water. The organic layer was dried (MgSO4) and concentrated to give crude product. The crude product was chromatographed (5% methanol in chloroform) on silica gel to give 8 mg of 7,9-dichloro-8-ethoxy- β-carboline.

Example 40 7-chloro-8-fluoro-β-carboline trifluoroacetate

[0073] A solution of the product of example 31 (78 mg, 0.42 mmol) in 1M HCl (1 ml) was treated with N-chlorosuccinimide (115 mg, 0.9 mmol) portionwise and the resulting mixture was stirred at 60 °C to 70 °C for 3h. The reaction was evaporated and the crude product purified by preparative HPLC using a C_{18}-packed column and eluting with a gradient (5:95 to 50:50) of water-acetonitril (with 0.1% trifluoroacetic acid). The pure fractions with product were combined and lyophilized to provide 33 mg of the title compound.

Example 41 1-hydroxy-7-trifluoromethyl-β-carboline and Example 42 7-tri-fluoromethyl-β-carboline

[0074] A solution of 3-hydroxy-2-piperdone (96 mg, 0.83 mmol) in methylene chloride (5 ml) was treated with Dess Martin reagent (352 mg, 0.85 mmol) at RT and the resulting mixture was stirred for 1h. After filtering the salts from the reaction, the ketone in solution was treated with 4-trifluoromethyl-phenylhydrazine (145 mg, 0.83 mmol). After 15 min, hexane (20 ml) was added and the hydrazone collected by filtration. This crude hydrazone was heated at 95 °C in formic acid (70%, 10 ml) for 1h. The reaction was evaporated and the residue was chromatographed (ethyl acetate) on silica gel to give 60 mg of dihydro 1-hydroxy-7-trifluoromethyl-β-carboline.

[0075] A portion of dihydro 1-hydroxy-7-trifluoromethyl-β-carboline (6 mg) in xylenes (1 ml) was treated with Pd/C (10%, 7 mg) and the mixture heated at 50 °C for one week. The reaction was concentrated after filtering it through celite, and the residue was chromatographed (1:1 hexane-ethyl acetate) on silica gel to give 1 mg of 1-hydroxy-7-trifluoromethyl-β-carboline.

[0076] A portion of dihydro 1-hydroxy-7-trifluoromethyl-β-carboline (25 mg) in THF (1 ml) was treated with a solution of lithium aluminum hydride in THF (1M, 0.5 ml). The reaction was stirred at 60 °C for 6h before quenching with water (5 ml) and extracting with ethyl acetate (3 times 10 ml). The combined organic layers were dried ($MgSO_4$) and concentrated to provide tetrahydro 7-trifluoromethyl-β-carboline. This material was taken up in xylenes (5 ml) and treated with Pd/C (10%, 15 mg). The mixture was stirred at 150 °C for 48h before filtering through celite and concentrating. The residue was chromatographed (ethyl acetate) on silica gel to give 5 mg of 7-tri-fluoromethyl-β-carboline.

Example 43 7-chloro-9-(methylamino)-β-carboline trifluoroacetate

[0077] A solution of the product of example 15 (50 mg, 0.23 mmol) in AcOH/methanol (1%, 3 ml) was treated with sodium cyanoborohydride (30 mg, 0.46 mmol) followed by formaldehyde (37%, 0.017 ml, 0.23 mmol). The reaction was stirred at RT for 36 h and then diluted with saturated $NaHCO_3$ (9 ml). After stirring for 15 min, the crude product was filtered and washed with water. The crude product was purified as described in example 46. The pure fractions with product were combined and lyophilized to provide 13 mg of the title compound.

Example 44 7-chloro-9-(dimethylamino)-β-carboline trifluoroacetate

[0078] A solution of the product of example 15 (50 mg, 0.23 mmol) in AcOH/methanol (1%, 3 ml) was treated with sodium cyanoborohydride (30 mg, 0.46 mmol) followed by formaldehyde (37%, 0.060 ml, 0.69 mmol). The reaction was stirred at RT for 36 h and then diluted with saturated $NaHCO_3$ (9 ml). After stirring for 15 min, the crude product was filtered and washed with water. The crude product was purified as described in example 46. The pure fractions with product were combined and lyophilized to provide 40 mg of the title compound.

Example 45 7-chloro-9-(methylsulfonylamino)-β-carboline trifluoroacetate

[0079] A solution of the product of example 15 (30 mg, 0.14 mmol) in pyridine (0.5 ml) was treated with methanesulfonyl chloride (0.024 ml, 0.30 mmol) in two portions over 30h. The reaction was diluted with water (5 ml) and the crude product collected and washed with water (several times). The crude product was purified as described in example 46.

The pure fractions with product were combined and lyophilized to provide 16 mg of the title compound.

Example 46 7-chloro-9-(propyionylamino)-β-carboline trifluoroacetate

[0080] A solution of the product of example 15 (30 mg, 0.14 mmol) in pyridine (1.0 ml) was treated with propionyl chloride (0.015 ml, 0.17 mmol). After stirring at RT for 4h, the reaction was diluted with water (9 ml) and saturated $NaHCO_3$ (1 ml). The crude product was collected and washed with water (several times). The crude product was purified by preparative HPLC using a C_{18}-packed column and eluting with a gradient (5:95 to 50:50) of water-acetonitril (with 0.1% trifluoroacetic acid). The pure fractions with product were combined and lyophilized to provide 21 mg of the title compound.

Example 47 7-chloro-9-(benzoylamino)-β-carboline trifluoroacetate

[0081] A solution of the product of example 15 (30 mg, 0.14 mmol) in pyridine (1.0 ml) was treated with benzoyl chloride (0.020 ml, 0.17 mmol). After stirring at RT for 4h, the reaction was diluted with water (9 ml) and saturated $NaHCO_3$ (1 ml). The crude product was collected and washed with water (several times). The crude product was purified as described in example 46. The pure fractions with product were combined and lyophilized to provide 12 mg of 7-chloro-9-(benzoylamino)-β-carboline trifluoroacetate.

Example 48 7-chloro-9-(Acetyl-methylamino)-β-carboline trifluoroacetate

[0082] A solution of the product of example 43 (19 mg, 0.082 mmol) in pyridine (0.40 ml) was treated with acetic anhydride (0.037 ml, 0.36 mmol) in two portions over 48h. The reaction was subsequently concentrated to dryness and the residue coevaporated with AcOH under reduced pressure. The crude product was purified as described in example 46. The pure fractions with product were combined and lyophilized to provide 9 mg of the title compound.

Example 49 7-chloro-9-(4-fluorobenzoylamino)-β-carboline trifluoroacetate

[0083] A solution of the product of example 15 (30 mg, 0.14 mmol) in pyridine (1.0 ml) was treated with 4-fluorobenzoyl chloride (0.018 ml, 0.17 mmol). After stirring at RT for 18h, the reaction was diluted with water (10 ml). The crude product was purified as described in example 46. The pure fractions with product were combined and lyophilized to provide 13 mg of the title compound.

Example 50

[0084] A cold (3 °C to 5 °C) solution of the product of example 15 (30 mg, 0.14 mmol) and pyridine (0.014 ml, 0.17 mmol) in THF (0.7 ml) was treated with phenyl chloroformate (0.018 ml, 0.145 mmol). After stirring at RT for 2h, the reaction was partitioned in ethyl acetate and buffer (pH 7.2). The organic layer was dried (brine, $Na2SO_4$) and concentrated to give 43 mg of phenyl carbamate. To a solution of phenyl carbamate (30 mg, 0.089 mmol) in DMSO (0.5 ml) was added 2-methoxyethylamine (0.010 ml, 0.10 mmol). After stirring at RT for 30 min, the crude reaction mixture was purified as described in example 46. The pure fractions with product were combined and lyophilized to provide 21 mg of the title compound.

Example 51 7-chloro-9-(methoxyacetylamino)-β-carboline trifluoroacetate

[0085] A solution of the product of example 15 (35 mg, 0.16 mmol) in pyridine (1.0 ml) was treated with methoxyacetyl chloride (0.016 ml, 0.18 mmol). After stirring at RT for 2h, the reaction was diluted with water (10 ml). The crude product was purified as described in example 46. The pure fractions with product were combined and lyophilized to provide 32 mg of the title compound.

Example 52 7-chloro-9-(3-methoxybenzoxylamino)-β-carboline trifluoroacetate

[0086] A solution of the product of example 15 (30 mg, 0.14 mmol) in pyridine (1.0 ml) was treated with m-anisoyl chloride (0.027 ml, 0.19 mmol) in two portions over 6h. The reaction was subsequently diluted with water (10 ml) and the crude product was purified as described in example 46. The pure fractions with product were combined and lyophilized to provide 33 mg of the title compound.

Example 53 7-chloro-9-(4-methoxybenzoxylamino)-β-carboline trifluoroacetate

[0087] A solution of the product of example 15 (30 mg, 0.14 mmol) in pyridine (1.0 ml) was treated with p-anisoyl chloride (37 mg, 0.22 mmol) in two portions over 24h. The reaction was subsequently diluted with water (10 ml) and the crude product was purified as described in example 46. The pure fractions with product were combined and lyophilized to provide 24 mg of the title compound.

Example 54 7-chloro-9-(methylcarbamylamino)-β-carboline trifluoroacetate

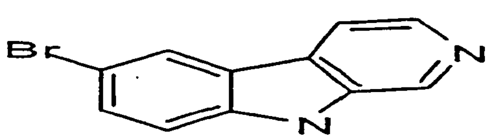
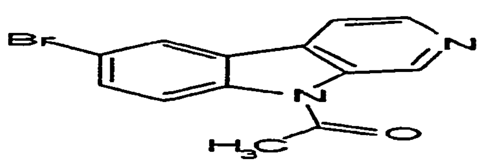
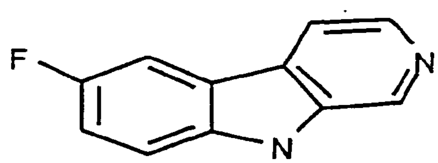
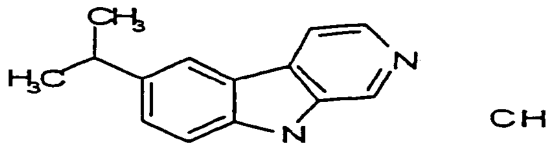
[0088] A solution of the product of example 15 (30 mg, 0.14 mmol) in pyridine (1.0 ml) was treated with p-anisoyl chloride (0.017 ml, 0.21 mmol) in two portions over 4h. The reaction was subsequently diluted with water (10 ml) and the crude product was purified as described in example 46. The pure fractions with product were combined and lyophilized to provide 35 mg of the title compound.

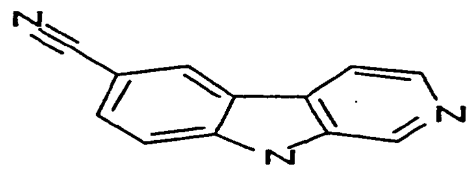
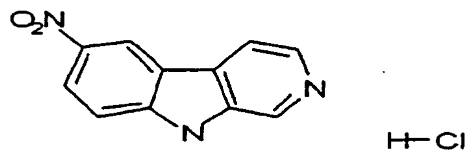
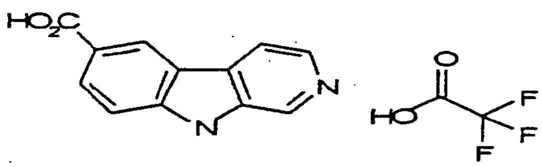
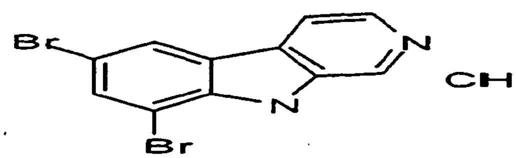
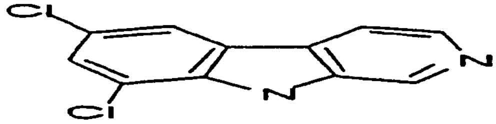
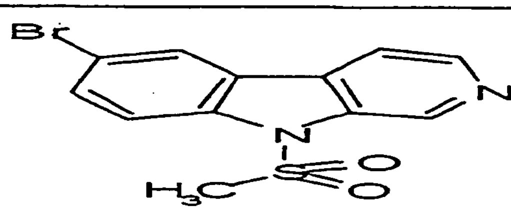
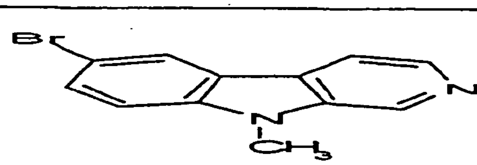
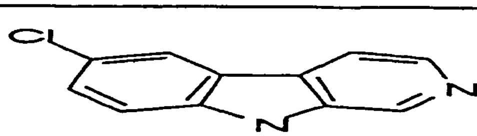
Example 55 7-chloro-9-(isovalerylamino)-β-carboline trifluoroacetate

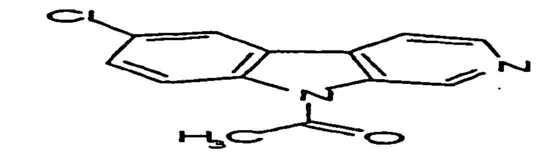
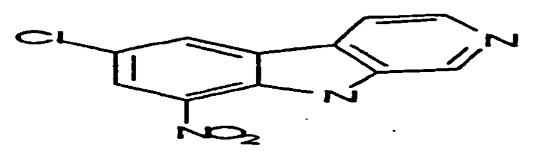
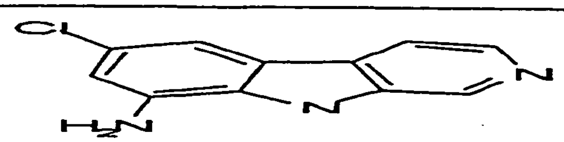
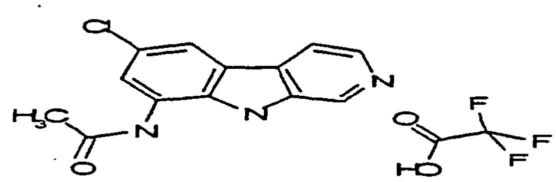
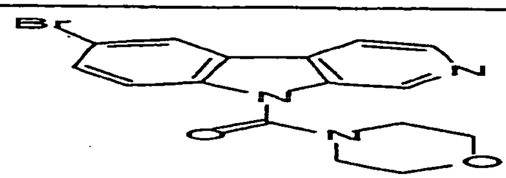
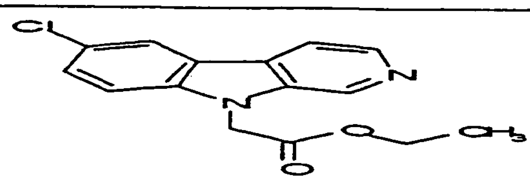
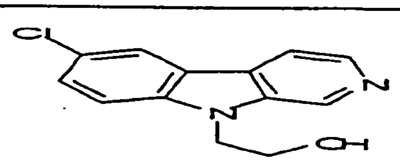
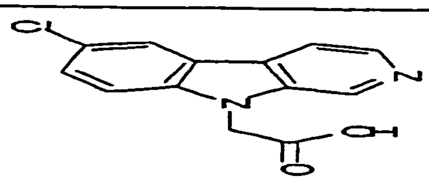
[0089] A solution of the product of example 15 (35 mg, 0.16 mmol) in pyridine (1.0 ml) was treated with isovalerylchloride (0.033 ml, 0.28 mmol) in two portions over 24h. The reaction was subsequently diluted with water (10 ml) and the crude product was purified as described in example 46. The pure fractions with product were combined and lyophilized to provide 52 mg of the title compound.

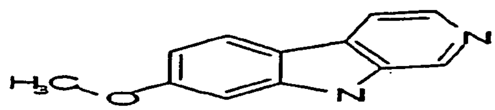
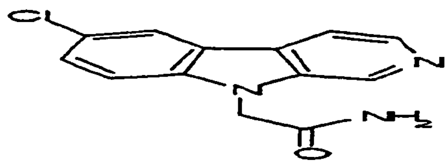
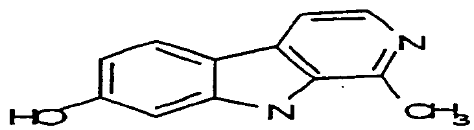
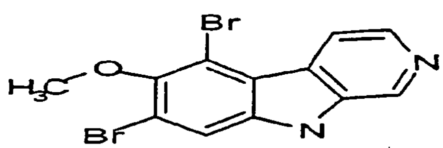
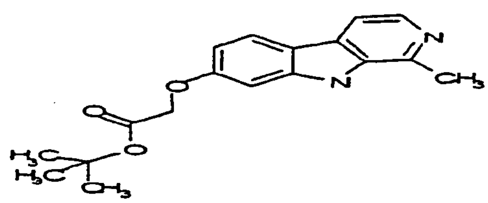
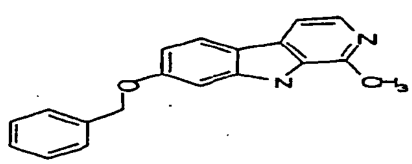
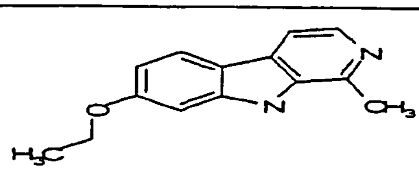
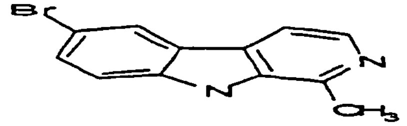
[0090] The examples in Table 1 show the structures of the prepared compounds.

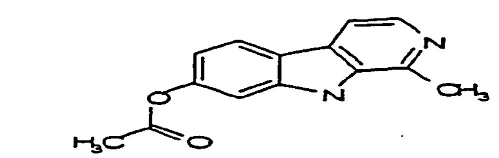
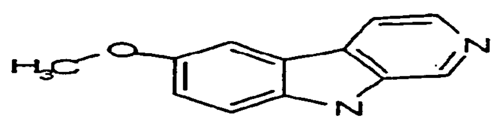
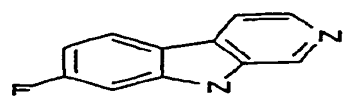
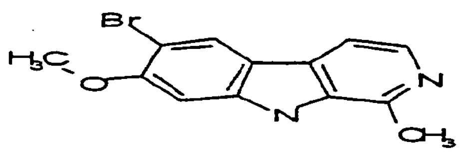
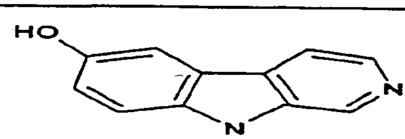
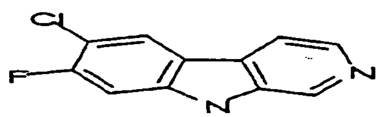
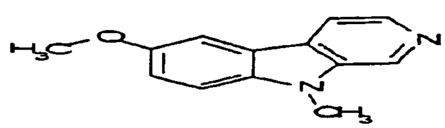
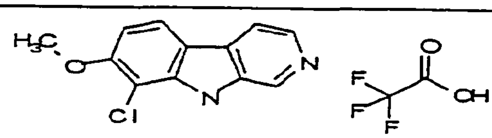
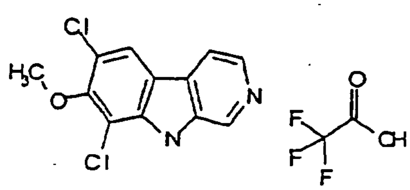
Table 1:

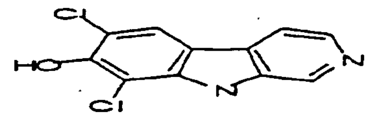
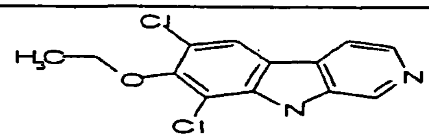
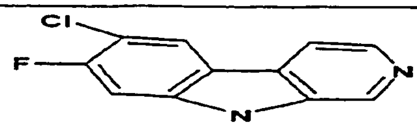
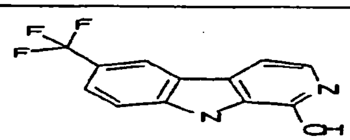
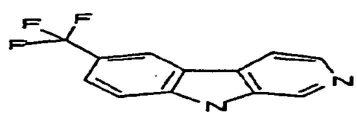
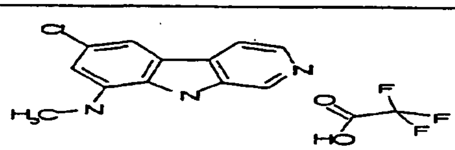
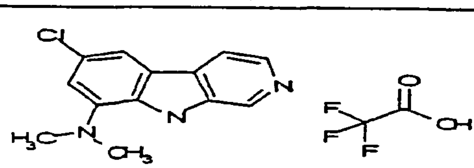
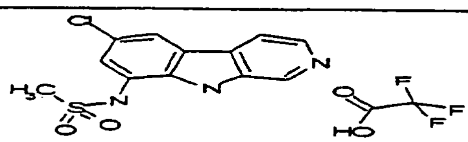
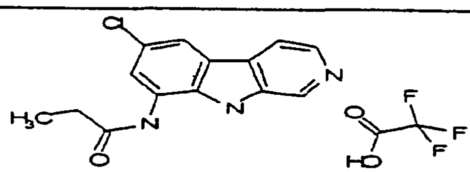
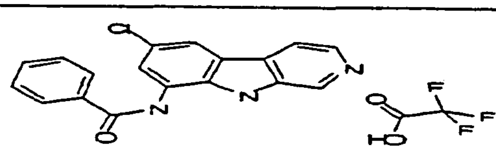
Example	Structure	Empirical formula	MS (M+ H)
1		$C_{11}H_7BrN_2$	248
2		$C_{13}H_9BrN_2O$	290
3		$C_{11}H_7FN_2$	187
4		$C_{14}H_{15}ClN_2$	211

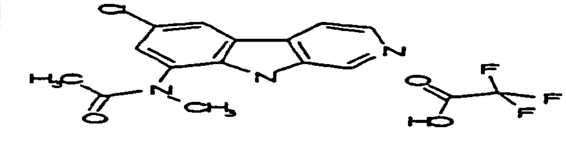
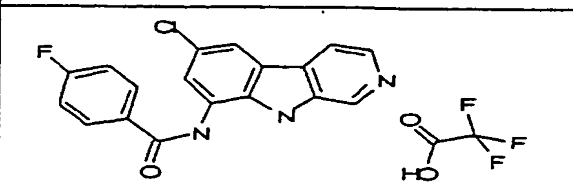
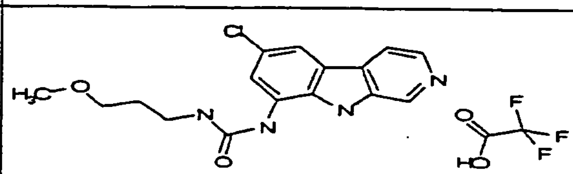
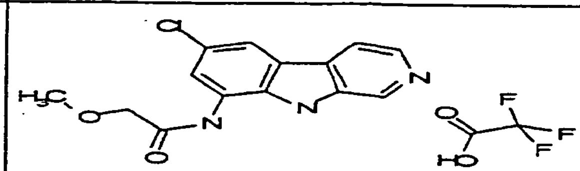
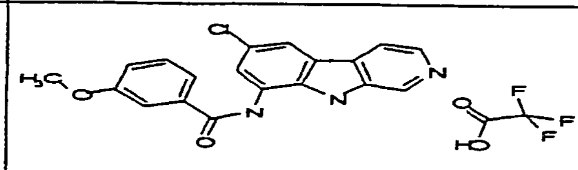
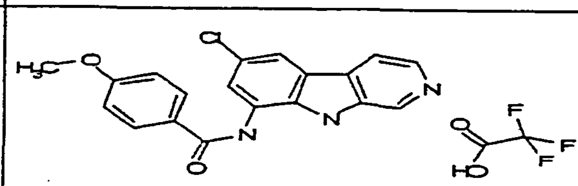
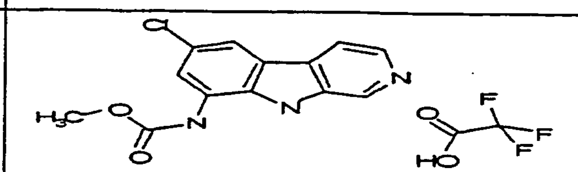
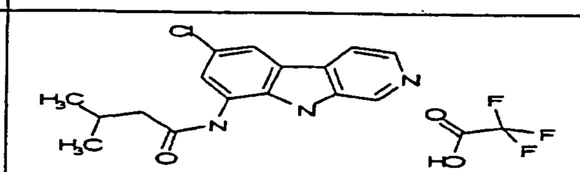
Example	Structure	Empirical formula	MS (M+ H)
5		$C_{12}H_7N_3$	194
6		$C_{11}H_8ClN_3O_2$	214
7		$C_{14}H_9F_3N_2O_4$	213
8		$C_{11}H_7Br_2ClN_2$	327
9		$C_{11}H_6Cl_2N_2$	238
10		$C_{12}H_9BrN_2O_2S$	326
11		$C_{12}H_9BrN_2$	262
12		$C_{11}H_7ClN_2$	204

Example	Structure	Empirical formula	MS (M+ H)
13		$C_{13}H_9ClN_2O$	246
14		$C_{11}H_6ClN_3O_2$	249
15		$C_{11}H_8ClN_3$	219
16		$C_{15}H_{11}ClF_3N_3O_3$	261
17		$C_{16}H_{14}BrN_3O_2$	361
18		$C_{15}H_{13}ClN_2O_2$	290
19		$C_{13}H_{11}ClN_2O$	248
20		$C_{13}H_9ClN_2O_2$	262

Example	Structure	Empirical formula	MS (M+ H)
21		$C_{12}H_{10}N_2O$	199
22		$C_{13}H_{10}ClN_3O$	261
23		$C_{12}H_{10}N_2O$	199
24		$C_{12}H_8Br_2N_2O$	257
25		$C_{18}H_{20}N_2O_3$	313
26		$C_{19}H_{16}N_2O$	289
27		$C_{14}H_{14}N_2O$	227
28		$C_{12}H_9BrN_2$	262

Example	Structure	Empirical formula	MS (M+ H)
29		$C_{14}H_{12}N_2O_2$	241
30		$C_{12}H_{10}N_2O$	199
31		$C_{11}H_7FN_2$	187
32		$C_{13}H_{11}BrN_2O$	292
33		$C_{11}H_8N_2O$	185
34		$C_{11}H_6ClFN_2$	222
35		$C_{13}H_{12}N_2O$	213
36			348
37			382

Example	Structure	Empirical formula	MS (M+ H)
38			254
39			282
40			222
41			253
42			237
43			347
44			361
45			411
46			389
47			437

Example	Structure	Empirical formula	MS (M+ H)
48			388
49			454
50			448
51			404
52			467
53			467
54			391
55			416

Pharmacological examples

IkB kinase ELISA

[0091] The in-vitro assay for detecting and measuring inhibition activity against IκBα-kinase complex by candidate pharmacological agents employs a biotinylated polypeptide spanning both Ser^{32} and Ser^{36} of IκBα and a specific antibody binding only to the phosphorylated form of the polypeptide, being either monoclonal or polyclonal (such as the commercially-available anti-phospho-serine^{32} IκBα antibodies from New England Biolabs, Beverly, MA, USA, cat. #9240). Once the antibody-phospho-polypeptide complex is formed, the complex can be detected by a variety of analytical methods utilizing such as radioactivity, luminescence, fluorescence or optical absorbance. For the use of the ELISA method, the complex can be immobilized either onto a biotin-binding plate (such as Neutravidin coated plate) and detected with a secondary antibody conjugated to HRP, or onto an antibody-binding plate (such as Protein-A coated plate) and detected with biotin-binding protein conjugated to HRP (such as Streptavidin-HRP). The level of activity can be correlated with a standard curve using synthetic phosphopeptides corresponding to the substrate polypeptide.

Experimental

[0092] IκBα kinase complex was prepared by first diluting 10 mL of HeLa S3 cell-extracts S100 fraction with 40 mL of 50 mM HEPES pH 7.5. Then, 40% ammonium sulfate was added and incubated on ice for 30 minutes. Precipitated pellet was redissolved with 5 mL of SEC buffer (50 mM HEPES pH 7.5, 1 mM DTT, 0.5 mM EDTA, 10 mM 2-glycerophosphate), clarified by centrifugation at 20,000 x g for 15 min., and filtration through a 0.22 μm filter unit. Sample was loaded onto a 320-mL Superose-6 FPLC column (Amersham Pharmacia Biotech AB, Uppsala, Sweden) equilibrated with SEC buffer operated at 2 mL/min flow rate at 4°C. Fractions spanning the 670-kDa molecular-weight marker were pooled for activation. Kinase-containing pool was then activated by incubating with 100 nM MEKK1Δ, 250 μM MgATP, 10 mM $MgCl_2$, 5 mM DTT, 10 mM 2-glycerophosphate, 2.5 μM Microcystin-LR, for 45 minutes at 37°C. Activated enzyme was stored at -80°C until further use.

[0093] Per well of a 96-well plate, compounds at various concentrations in 2 μL DMSO were pre-incubated for 30 minutes at 25°C with 43 μL of activated enzyme diluted [1:25] with assay buffer (50 mM HEPES pH 7.5, 5 mM DTT, 10 mM $MgCl_2$, 10 mM 2-glycerophosphate, 2.5 μM Microcystin-LR). Five microliters of peptide substrate (biotin-$(CH_2)_6$-DRHDSGLDSMKD-$CONH_2$) at 200 μM stock solution was added to each well and incubated for 1 hour before quenching with 150 μL of 50 mM HEPES pH 7.5, 0.1% BSA, 50 mM EDTA, plus [1:200] antibody. Quenched kinase reaction samples and phosphopeptide-calibration standards (biotin-$(CH_2)_6$- DRHDS$[PO_3]$GLDSMKD-$CONH_2$, serially diluted in assay buffer) at 100 μL per well were transferred to a Protein-A plate (Pierce Chemical Co., Rockford, IL, USA) and incubated for 2 hours. with shaking. Following 3 washes with PBS, 100 μL of 0.5 μg/mL Streptavidin conjugated with HRP (horseradish peroxidase) diluted with 50 mM HEPES/ 0.1% BSA, was added for 30 minutes. After 5 washes with PBS, 100 μL TMB substrate (Kirkegaard & Perry Laboratories, Gaithersburg, MD, USA) was added and color development was stopped by adding 100 μL of 0.18 M H_2SO_4. Absorbance signals were recorded at 450 nm. Calibrationcurve standards were fitted by linear regression using a 4-parameter dose-response equation. Based on this standard curve, levels of kinase activity were calculated in order to determine inhibition activity of candidate pharmacological agents. Table 3 which follows shows the results.

Table 3:

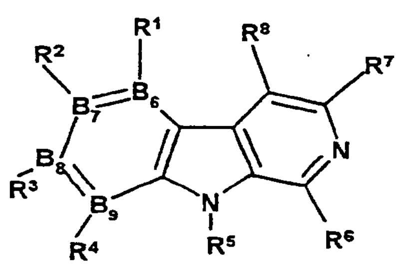
Kinase inhibition at a substance concentration of IC_{50} in μM					
Example number	IkB-kinase IC_{50}	Example number	IkB-kinase IC_{50}	Example number	IkB-kinase IC_{50}
1	0.4	10	0.4	19	3
2	0.4	11	0.7	20	14
3	1	12	0.4	21	1.8
4	2.5	13	0.5	22	15
5	1	14	4	23	22
6	3	15	0.8	24	4.6
7	65	16	0.3	25	31

Table 3: (continued)

Kinase inhibition at a substance concentration of IC_{50} in μM					
Example number	IkB-kinase IC_{50}	Example number	IkB-kinase IC_{50}	Example number	IkB-kinase IC_{50}
8	0.2	17	5	26	12
9	0.2	18	23	27	4.5
28	11	40	2	52	0.6
29	40	41	2.2	53	1.4
30	5.2	42	0.8	54	0.7
31	3.3	43	1	55	0.8
32	4.6	44	2		
33	1.5	45	8.3		
34	1	46	0.3		
35	3.5	47	0.6		
36	1.4	48	4		
37	0.15	49	0.22		
38	11	50	10		
39	0.1	51	0.6		

Claims

1. A compound of the formula I



(I)

and/or a stereoisomeric form of the compounds of the formula I and/or a physiologically tolerable salt of the compounds of the formula I, where B_6, B_7, B_8 and B_9 are independently selected from the group consisting of carbon atom and nitrogen atom, where B_6, B_7, B_8 and B_9 together are no more than two nitrogen atoms at the same time; where the substituents R^1, R^2, R^3, R^4 and R^8 independently of one another are

1. hydrogen atom,
2. halogen,
3. -OH,
4. -CN,
5. sulfo,
6. $-NO_2$,
7. $-NH_2$,
8. alkoxy,
9. substituted amino,

10. -COOH,
11. $-O-R^{10}$, wherein R^{10} is alkyl, substituted alkyl or aryl,
12. $-C(O)-R^{12}$, wherein R^{12} is alkyl, substituted alkyl or aryl,
13. $-C(O)-O-R^{12}$, wherein R^{12} is as defined above,
14. aryl,
15. -O-aryl,
16. substituted aryl,
17. -O-substituted aryl,
18. alkyl,
19. substituted alkyl,
20. $-CF_3$ or
21. $-CF_2-CF_3$,

provided that at least one of R^1, R^2, R^3, R^4 and R^8 is not a hydrogen atom,
R^5 is

1. hydrogen atom,
2. alkyl,
3. alkyl radical, substituted at one or more positions by one ormore of the radicals, halogen, amino or hydroxyl,
4. $-C(O)-R^9$ or
5. $-S(O)_2-R^9$, in which
R^9 is

a) alkyl,
b) alkyl radical, substituted at one or more positions by one or more of the radicals, halogen, amino or hydroxyl,
c) aryl,
d) aryl radical, substituted at one or more positions by one or more of the radicals, halogen, amino, or hydroxyl,
e) $-NH_2$,
f) alkoxy or
g) substituted amino, and

R^6 and R^7 independently of one another are

1. hydrogen atom,
2. halogen,
3. -OH,
4. methyl,
5. $-O-(C_1-C_{10})$-alkyl, wherein alkyl is unsubstituted or mono- to trisubstituted independently of one another by

5.1 aryl,
5.2 halogen,
5.3 $-NO_2$,
5.4 sulfo,
5.5 -COOH,
5.6 $-NH_2$,
5.7 $-O-(C_1-C_4)$-alkyl or
5.8 -OH, or

6. $-N(R^{13})_2$, wherein R^{13} is independently of one another hydrogen atom, aryl, $-C(O)-(C_1-C_4)$-alkyl or substituted aryl or alkyl, wherein alkyl is unsubstituted or mono- to tri- substituted independently of one another as defined under 5.1 to 5.8, or R^{13} together with nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,

provided that a compound of the formula I, where R^1 is Br, R^2 is $-O-C(O)CH_3$, R^5 is $-C(O)CH_3$, R^3, R^4, R^6, R^7 and R^8 together are each hydrogen atom and B_6, B_7, B_8 and B_9 together are each carbon atom is excluded; a compound of the formula I, where R^2 is $-O-C(O)CH_3$, R^3 is Br, R^5 is $-C(O)CH_3$, R^1, R^4, R^6, R^7 and R^8 together are each

hydrogen atom and B_6, B_7, B_8 and B_9 together are each carbon atom is excluded; a compound of the formula I, where R^2 is Br, R^1, R^3, R^4, R^5, R^6, R^7 and R^8 together are each hydrogen atom and B_6, B_7, B_8 and B_9 together are each carbon atom is excluded; a compound of the formula I, where R^3 is Br, R^1, R^2, R^4, R^5, R^6, R^7 and R^8 together are each hydrogen atom and B_6, B_7, B_8 and B_9 together are each carbon atom is excluded

2. A compound of the formula I as claimed in Claim 1, wherein B_6, B_7, B_8, and B_9 are each a carbon atom, R^1, R^2, R^3, R^4 and R^8 independently of one another are

1. hydrogen atom,
2. halogen,
3. -CN,
4. -COOH,
5. $-NO_2$,
6. $-NH_2$,
7. -O-(C_1-C_{10})-alkyl, wherein alkyl is mono- to penta- substituted independently of one another by

   7.1 phenyl, which is unsubstituted or mono- to pentasubstituted by halogen or -O-(C_1-C_4)-alkyl,
   7.2 halogen,
   7.3 $-NH_2$,
   7.4 -OH,
   7.5 -COOH,
   7.6 $-NO_2$,
   7.7 -S(O)$_y$-R^{14}, wherein y is zero, 1 or 2, R^{14} is -(C_1-C_{10})-alkyl, phenyl, which is unsubstituted or mono- to pentasubstituted as defined for substituents under 7.1 to 7.9, amino or -N(R^{13})$_2$, wherein R^{13} is independently of one another hydrogen atom, phenyl, -(C_1-C_{10})-alkyl, -C(O)-(C_1-C_7)-alkyl, -C(O)-phenyl, -C(O)-NH-(C_1-C_7)-alkyl, -C(O)-O-phenyl, -C(O)-NH-phenyl, -C(O)-O-(C_1-C_7)-alkyl, -S(O)$_y$-R^{14}, wherein R^{14} and y are as defined above,
   and wherein alkyl or phenyl in each case are unsubstituted or mono- to penta- substituted independently of one another as defined under 7.1 to 7.9 above, or
   R^{13} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,
   7.8 -O-(C_1-C_{10})-alkyl or
   7.9 -O-phenyl,

8. -N(R^{13})$_2$, wherein R^{13} is as defined in 7.7 above,
9. -S(O)y-R^{14}, wherein R^{14} and y are as defined in 7.7 above,
10. -C(O)-R^{12}, wherein R^{12} is phenyl or -(C_1-C_7)-alkyl, wherein alkyl or phenyl are unsubstituted or mono- to penta- substituted independently of one another as defined under 7.1 to 7.9 above,
11. -C(O)-O-R^{12}, wherein R^{12} is as defined in 10. above,
12. -(C_1-C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to pentasubstituted independently of one another as defined under 7.1 to 7.9 above,
13. $-CF_3$ or
14. $-CF_2$-CF_3,

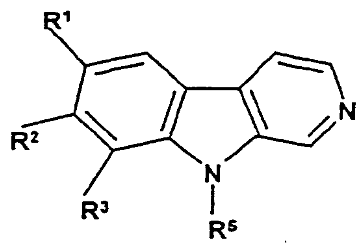
provided that at least one of R^1, R^2, R^3, R^4 and R^8 is not a hydrogen atom, R^5 is

1. hydrogen atom,
2. -(C_1-C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to penta- substituted independently of one another as defined under 7.1 to 7.4 above,
3. -C(O)-R^9, wherein R^9 is
   $-NH_2$, -(C_1-C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to penta- substituted independently of one another as defined under 7.1 to 7.4, or -N(R^{13})$_2$, wherein R^{13} is as defined in 7.7 above, or
4. -S(O)$_2$-R^9, wherein R^9 is as defined in 3 above.

3. A compound of the formula I as claimed in claim 1 or 2, wherein B_6, B_7, B_8, and B_9 are each a carbon atom, R^1, R^2, R^3 and R^4 independently of one another are hydrogen atom, halogen, cyano, nitro, amino, -O-(C_1-C_7)-alkyl, phenyl, -O-phenyl, $-CF_3$, $-CF_2$-CF_3, N(R^{13})$_2$,
wherein R^{13} is independently of one another hydrogen atom, -(C_1-C_7)-alkyl, phenyl, -C(O)-phenyl, -C(O)-

NH-phenyl, -C(O)-O-phenyl, -C(O)-O-(C_1-C_4)-alkyl, -C(O)-(C_1-C_7)-alkyl or -(C_1-C_{10})-alkyl, wherein alkyl or phenyl are unsubstituted or mono- to trisubstituted independently of one another as defined under 7.1 to 7.9, or R^{13} together with nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,
$S(O)_y$-R^{14}, wherein y is zero, 1 or 2, and R^{14} is -(C_1-C_{10})-alkyl, phenyl,
which is unsubstituted or mono- to penta- substituted as defined for substituents under 7.1 to 7.9, amino or -$N(R^{13})_2$,
wherein R^{13} is as defined above,
wherein alkyl is unsubstituted or mono- to tri- substituted independently of one another as defined under 7.1 to 7.9, or
-C(O)-O-R^{12}, wherein R^{12} is as defined above,
R^6, R^7 and R^8 independently of one another are hydrogen atom, methyl, amino, -$N(R^{13})_2$, wherein R^{13} is as defined above,
provided that at least one of R^1, R^2, R^3, R^4 and R^8 is not a hydrogen atom, and R^5 is as defined in claim 2.

4. A compound of the formula II



(II)

and/or a stereoisomeric form of the compound of the formula II and/or a physiologically tolerable salt of the compound of the formula II, as claimed in any one of claims 1 to 3, wherein;
R^1, R^2 and R^3 are independently from one another hydrogen atom, halogen, cyano, amino, -O-(C_1-C_4)-alkyl, nitro, -CF_3, -CF_2-CF_3, -$S(O)_y$-R^{14}, wherein y is 1 or 2, R^{14} is amino, -(C_1-C_7)-alkyl, phenyl,
which is unsubstituted or mono- to tri- substituted as defined for substituents under 7.1 to 7.9, or -$N(R^{13})_2$,
wherein R^{13} is independently of one another hydrogen atom, -(C_1-C_7)-alkyl -C(O)-(C_1-C_7)-alkyl, -C(O)-phenyl, -C(O)-O-phenyl, -C(O)-O-(C_1-C_4)-alkyl or -(C_1-C_{10})-alkyl, wherein alkyl or phenyl are unsubstituted or mono- to tri- substituted independently of one another as defined under 7.1 to 7.9, or R^{13} together with nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,
-C(O)-NH-(C_1-C_4)-alkyl, -C(O)-O-(C_1-C_4)-alkyl or -(C_1-C_{10})-alkyl, wherein alkyl in each case is unsubstituted or mono- to tri- substituted independently of one another as defined under 7.1 to 7.9,
provided that at least one of R^1, R^2 and R^3 is not a hydrogen atom, and
R^5 is hydrogen atom, -(C_1-C_{10})-alkyl,
wherein alkyl is unsubstituted or mono- to tri- substituted independently of one another as defined under 7.1 to 7.4, -C(O)-R^9 or -$S(O)_2$-R^9, wherein
R^9 is -(C_1-C_{10})-alkyl, -O-(C_1-C_{10})-alkyl,
wherein alkyl is unsubstituted or mono- to tri- substituted independently of one another as defined under 7.1 to 7.4, phenyl, which is unsubstituted or mono- to tri- substituted as defined under 7.1 to 7.9, or -$N(R^{13})_2$,
wherein R^{13} is as defined above,
provided that a compound of the formula II, where R^1 is Br and R^2, R^3 and R^5 are each a hydrogen atom is excluded and a compound of the formula II, where R^2 is Br and R^2, R^3 and R^5 are each a hydrogen atom is excluded.

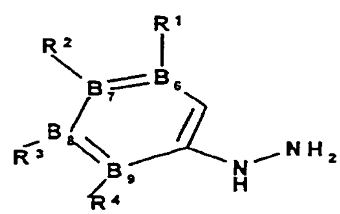
5. A compound of the formula II as claimed in claim 4, wherein
R^1, R^2 and R^3 are independently from each other hydrogen atom, halogen, cyano, amino, -O-(C_1-C_4)-alkyl, nitro, -CF_3 or $N(R^{13})_2$,
wherein R^{13} is independently of one another hydrogen atom, -(C_1-C_7)-alkyl, -C(O)-(C_1-C_7)-alkyl, -C(O)-phenyl or -C(O)-O-(C_1-C_4)-alkyl, wherein alkyl or phenyl are unsubstituted or mono- to tri- substituted independently of one another by halogen or -O-(C_1-C_4)-alkyl, and
R^5 is hydrogen atom, -C(O)-CH_3, methyl, -CH_2-CH_2-OH, -$S(O)_2$-CH_3, -C(O)-morpholinyl or -CH_2-C(O)-NH_2, provided that no more than two of R^1, R^2, R^3 and R^5 are a hydrogen atom.

6. A compound of the formula II as claimed in any one of claims 4 or 5, wherein R^1 is is bromo, $-CF_3$ or chloro, R^2 is hydrogen atom or O-(C_1-C_2)-alkyl,
R^3 is hydrogen atom, bromo, chloro or $-N(R^{13})_2$,
wherein R^{13} is independently of one another hydrogen atom, -C(O)-phenyl, -(C_1-C_7)-alkyl, -C(O)-(C_1-C_4)-alkyl or -C(O)-O-(C_1-C_4)-alkyl, wherein alkyl or phenyl are unsubstituted or mono- to tri- substituted independently of one another by halogen or -O-(C_1-C_2)-alkyl, and
R^5 is hydrogen atom, $-C(O)-CH_3$, methyl or $-S(O)_2-CH_3$.

7. A compound of the formula II as claimed in any one of claims 4 to 6, R^1 is chloro, R^2 and R^3 are each hydrogen atom, and R^5 is $-C(O)-CH_3$, or R^1 is bromo, R^5 is $-C(O)-CH_3$ and R^2 and R^3 are each hydrogen atom, or R^1 is chloro, R^3 is $-N-C(O)-CH_2-O-CH_3$ and R^2 and R^5 are each hydrogen atom, or R^1 is chloro, R^3 is -N-C(O)-para-fluoro-phenyl and R^2 and R^5 are each hydrogen atom, or R^1 and R^3 are each chloro, R^2 is-$C(O)-CH_3$ and R^5 is hydrogen atom, or R^1 and R^3 are each chloro, R^5 is hydrogen atom and R^2 is $-C(O)-CH_2-CH_3$.

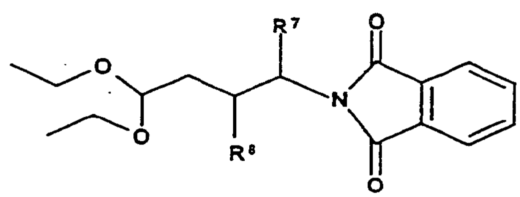
8. A process for the preparation of the compounds of the formula I as claimed in any one of claims 1 to 7, which comprises

a) reacting a compound of formula III



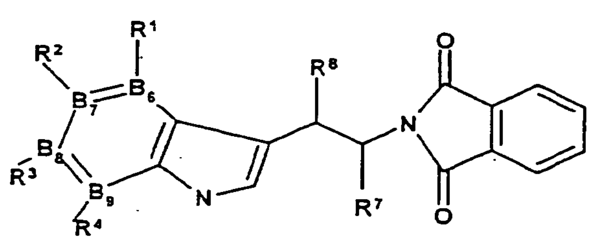
(III)

in which R^1, R^2, R^3, R^4, B_6, B_7, B_8 and B_9 are each as defined in formula I, with a compound of the formula IV,



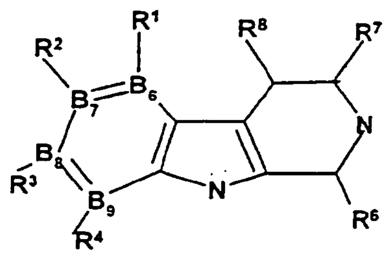
(IV)

in the presence of a acid, converting into a compound of the formula V,



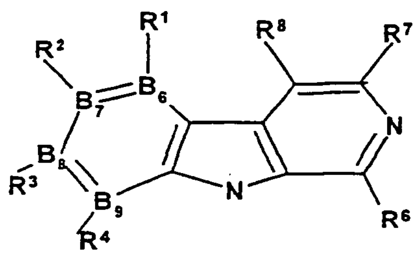
(V)

and is reacted with hydrazine hydrate and later with formaldehyde (R^6 is H) or R^6CHO to give a compound of formula VI



(VI)

and oxidized to give a compound of the formula VII,



(VII)

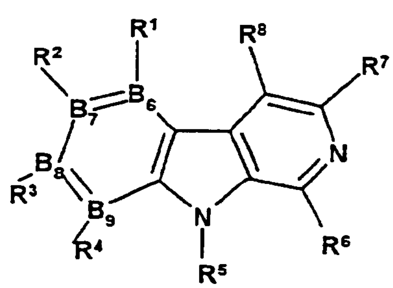
where R^1 to R^4 and B_6 to B_9 are as defined in formula I and R^5 is hydrogen atom, or
b) a compound of the formula VII is reacted with a compound of the formula VIII

$$Y\text{-}R^5 \quad \text{(VIII)}$$

where Y is halogen or -OH and R^5 is as defined in formula I, to give a compound of the formula I, or
c) resolving a compound of the formula I, which on account of its chemical structure occurs in enantiomeric forms, prepared by process a) or b) into the pure enantiomers by salt formation with enantiomerically pure acids or bases, chromatography on chiral stationary phases or derivatization by means of chiral enantiomerically pure compounds such as amino acids, separation of the diastereomers thus obtained, and removal of the chiral auxiliary groups, or
d) isolating the compound of the formula I prepared by process a), b) or c) either in free form or, in the case of the presence of acidic or basic groups, converting it into physiologically tolerable salts.

9. A pharmaceutical which comprise an efficacious amount of at least one compound of the formula I as claimed in any one of claims 1 to 7 and/or of a physiologically tolerable salt of the compounds of the formula I and/or an optionally stereoisomeric form of the compounds of the formula I, together with a pharmaceutically suitable and physiologically tolerable excipient, additive and/or other active compounds and auxiliaries.

10. The use of the compound of the formula I



(I)

and/or a stereoisomeric form of the compounds of the formula I and/or a physiologically tolerable salt of the compounds of the formula I,
for the production of pharmaceuticals for the prophylaxis and therapy of disorders in whose course an increased activity of I_kB kinase is involved,
where B_6, B_7, B_8 and B_9 are independently selected from the group consisting of carbon atom and nitrogen atom, where B_6, B_7, B_8 and B_9 are no more than two nitrogen atoms at the same time;
where the substituents R^1, R^2, R^3, R^4 and R^8 independently of one another are

1. hydrogen atom,
2. halogen,
3. -OH,
4. -CN,
5. sulfo,
6. $-NO_2$,
7. $-NH_2$,
8. alkoxy,
9. substituted amino,
10. -COOH,
11. $-O-R^{10}$, wherein R^{10} is alkyl, substituted alkyl or aryl,
12. $-C(O)-R^{12}$, wherein R^{12} is alkyl, substituted alkyl or aryl,
13. $-C(O)-O-R^{12}$, wherein R^{12} is as defined above,
14. aryl,
15. -O-aryl,
16. substituted aryl,
17. -O-substituted aryl,
18. alkyl,
19. substituted alkyl,
20. $-CF_3$ or
21. $-CF_2-CF_3$,

provided that at least one of R^1, R^2, R^3, R^4 and R^8 is not a hydrogen atom,
R^5 is

1. hydrogen atom,
2. alkyl,
3. alkyl radical, substituted at one or more positions by one or more of the radicals, halogen, amino or hydroxyl,
4. $-C(O)-R^9$ or
5. $-S(O)_2-R^9$, in which
   R^9 is

   a) alkyl,
   b) alkyl radical, substituted at one or more positions by one or more of the radicals, halogen, amino or hydroxyl,
   c) aryl,
   d) aryl radical, substituted at one or more positions by one or more of the radicals, halogen, amino, or hydroxyl,
   e) $-NH_2$,
   f) alkoxy or
   g) substituted amino, and

R^6 and R^7 independently of one another are

1. hydrogen atom,
2. halogen,
3. -OH,
4. methyl,
5. $-O-(C_1-C_{10})$-alkyl, wherein alkyl is unsubstituted or mono- to trisubstituted independently of one another by

5.1 aryl,
5.2 halogen,
5.3 $-NO_2$,
5.4 sulfo,
5.5 -COOH,
5.6 $-NH_2$,
5.7 -O-(C_1-C_4)-alkyl or
5.8 -OH, or

6. $N(R^{13})_2$, wherein R^{13} is independently of one another hydrogen atom, aryl, -C(O)-(C_1-C_4)-alkyl or substituted aryl or alkyl, wherein alkyl is unsubstituted or mono- to tri- substituted independently of one another as defined under 5.1 to 5.8, or R^{13} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms.

11. The use of the compound of the formula I as claimed in claim 10, wherein B_6, B_7, B_8; and B_9 are each a carbon atom, R^1, R^2, R^3, R^4 and R^8 independently of one another are

1. hydrogen atom,
2. halogen,
3. -CN,
4. -COOH,
5. $-NO_2$,
6. $-NH_2$,
7. -O-(C_1-C_{10})-alkyl, wherein alkyl is mono- to penta- substituted independently of one another by

7.1 phenyl, which is unsubstituted or mono- to pentasubstituted by halogen or -O-(C_1-C_4)-alkyl,
7.2 halogen,
7.3 $-NH_2$,
7.4 -OH,
7.5 -COOH,
7.6 $-NO_2$,
7.7 $-S(O)_y-R^{14}$, wherein y is zero, 1 or 2, R^{14} is -(C_1-C_{10})-alkyl, phenyl, which is unsubstituted or mono- to pentasubstituted as defined for substituents under 7.1 to 7.9, amino or $-N(R^{13})_2$, wherein R^{13} is independently of one another hydrogen atom, phenyl, -(C_1-C_{10})-alkyl, -C(O)-(C_1-C_7)-alkyl, -C(O)-phenyl, -C(O)-NH-(C_1-C_7)-alkyl, -C(O)-O-phenyl, -C(O)-NH-phenyl, -C(O)-O-(C_1-C_7)-alkyl, $-S(O)_y-R^{14}$, wherein R^{14} and y are as defined above,
and wherein alkyl or phenyl in each case are unsubstituted or mono- to penta- substituted independently of one another as defined under 7.1 to 7.9 above, or
R^{13} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,
7.8 -O-(C_1-C_{10})-alkyl or
7.9 -O-phenyl,

8. $-N(R^{13})_2$, wherein R^{13} is as defined in 7.7 above,
9. $-S(O)y-R^{14}$, wherein R^{14} and y are as defined in 7.7 above,
10. $-C(O)-R^{12}$, wherein R^{12} is phenyl or -(C_1-C_7)-alkyl, wherein alkyl or phenyl are unsubstituted or mono- to penta- substituted independently of one another as defined under 7.1 to 7.9 above,
11. $-C(O)-O-R^{12}$, wherein R^{12} is as defined under 10. above,
12. -(C_1-C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to pentasubstituted independently of one another as defined under 7.1 to 7.9 above,
13. $-CF_3$ or
14. $-CF_2-CF_3$,

provided that at least one of R^1, R^2, R^3, R^4 and R^8 is not a hydrogen atom,
R^5 is

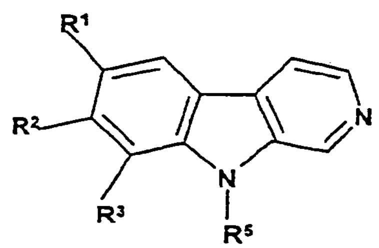
1. hydrogen atom,
2. -(C_1-C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to penta- substituted independently of one another as defined under 7.1 to 7.4 above,

3. -C(O)-R^9, wherein R^9 is
-NH_2, -(C_1-C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to penta- substituted independently of one another as defined under 7.1 to 7.4, or -$N(R^{13})_2$, wherein R^{13} is as defined in 7.7 above, or
4. -$S(O)_2$-R^9, wherein R^9 is as defined in 3 above, and

R^6 and R^7 independently of one another are hydrogen atom or methyl.

12. The use of the compound of the formula I as claimed in claims 10 or 11, wherein B_6, B_7, B_8, and B_9 are each a carbon atom,
R^1, R^2, R^3 and R^4 independently of one another are hydrogen atom, halogen, cyano, nitro, amino, -O-(C_1-C_7)-alkyl, phenyl, -O-phenyl, -CF_3, -CF_2-CF_3, -$N(R^{13})_2$,
wherein R^{13} is independently of one another hydrogen atom, -(C_1-C_7)-alkyl, phenyl, -C(O)-phenyl, -C(O)-NH-phenyl, -C(O)-O-phenyl, -C(O)-O-(C_1-C_4)-alkyl, -C(O)-(C_1-C_7)-alkyl or -(C_1-C_{10})-alkyl, wherein alkyl or phenyl are unsubstituted or mono- to trisubstituted independently of one another as defined under 7.1 to 7.9, or R^{13} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,
$S(O)_y$-R^{14}, wherein y is zero, 1 or 2, and R^{14} is -(C_1-C_{10})-alkyl, phenyl, which is unsubstituted or mono- to penta-substituted as defined for substituents under 7.1 to 7.9, amino or -$N(R^{13})_2$, wherein
R^{13} is as defined above,
wherein alkyl is unsubstituted or mono- to tri- substituted independently of one another as defined under 7.1 to 7.9, or -C(O)-O-R^{12}, wherein R^{12} is as defined in claim 11,
R^6, R^7 and R^8 independently of one another are hydrogen atom, methyl, amino, -$N(R^{13})_2$, wherein R^{13} is as defined above,
provided that at least one of R^1, R^2, R^3, R^4 and R^8 is not a hydrogen atom, and R^5 is as defined in claim 11.

13. The use of the compound of the formula II



(II)

as claimed in any one of claims 10 to 12, and/or a stereoisomeric form of the compounds of the formula II and/or a physiologically tolerable salt of the compounds of the formula II, for the production of pharmaceuticals for the prophylaxis and therapy of disorders in whose course an increased activity of I_kB kinase is involved, wherein;
R^1, R^2 and R^3 are independently from each other hydrogen atom, halogen, cyano, amino, -O-(C_1-C_4)-alkyl, nitro, -CF_3, -CF_2-CF_3, -$S(O)_y$-R^{14}, wherein y is 1 or 2, R^{14} is amino, -(C_1-C_7)-alkyl, phenyl, which is unsubstituted or mono- to tri- substituted as defined for substituents under 7.1 to 7.9, or -$N(R^{13})_2$,
wherein R^{13} is independently of one another hydrogen atom, -(C_1-C_7)-alkyl -C(O)-(C_1-C_7)-alkyl, -C(O)-phenyl, -C(O)-O-phenyl, -C(O)-O-(C_1-C_4)-alkyl or -(C_1-C_{10})-alkyl, wherein alkyl or phenyl are unsubstituted or mono- to trisubstituted independently of one another as defined under 7.1 to 7.9, or
R^{13} together with nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,
-C(O)-NH-(C_1-C_4)-alkyl, -C(O)-O-(C_1-C_4)-alkyl or -(C_1-C_{10})-alkyl, wherein alkyl in each case is unsubstituted or mono- to tri- substituted independently of one another as defined under 7.1 to 7.9, provided that at least one of R^1, R^2 and R^3 is not a hydrogen atom, and
R^5 is hydrogen atom, -(C_1-C_{10})-alkyl,
wherein alkyl is unsubstituted or mono- to tri- substituted independently of one another as defined under 7.1 to 7.4, -C(O)-R^9 or -$S(O)_2$-R^9, wherein
R^9 is -(C_1-C_{10})-alkyl, -O-(C_1-C_{10})-alkyl,
wherein alkyl is unsubstituted or mono- to tri- substituted
independently of one another as defined under 7.1 to 7.4,
phenyl, which is unsubstituted or mono- to tri- substituted as defined under 7.1 to 7.9, or -$N(R^{13})_2$,
wherein R^{13} is as defined above.

14. The use of the compound of the formula II as claimed in any one of claims 10 to 13, wherein R^1, R^2 and R^3 are independently from one another hydrogen atom, halogen, cyano, amino, -O-(C_1-C_4)-alkyl, nitro, -CF_3 or $N(R^{13})_2$,
wherein R^{13} is independently of one another hydrogen atom, -(C_1-C_7)-alkyl, -C(O)-(C_1-C_7)-alkyl, -C(O)-phenyl or -C(O)-O-(C_1-C_4)-alkyl, wherein alkyl or phenyl are unsubstituted or mono- to tri- substituted independently of one another by halogen or -O-(C_1-C_4)-alkyl, and
R^5 is hydrogen atom, -C(O)-CH_3, methyl, -$S(O)_2$-CH_3, -CH_2-CH_2-OH, -C(O)-morpholinyl or -CH_2-C(O)-NH_2, provided that no more than two of R^1, R^2, R^3 and R^5 are a hydrogen atom.

15. The use of the compound of the formula II as claimed in any one of claims 10 to 14, wherein R^1 is bromo, -CF_3 or chloro, R^2 is hydrogen atom or O-(C_1-C_2)-alkyl, R^3 is hydrogen atom, bromo, chloro or -N $(R^{13})_2$,
wherein R^{13} is independently of one another hydrogen atom, -C(O)-phenyl, -(C_1-C_7)-alkyl, -C(O)-(C_1-C_4)-alkyl or -C(O)-O-(C_1-C_4)-alkyl, wherein alkyl or phenyl are unsubstituted or mono- to tri- substituted independently of one another by halogen or -O-(C_1-C_2)-alkyl, and
R^5 is hydrogen atom, -C(O)-CH_3, methyl or -$S(O)_2$-CH_3.

16. The use of the compound of the formula II as claimed in any one of claims 10 to 15, wherein R^1 is chloro, R^2 and R^3 are each hydrogen atom, and R^5 is -C(O)-CH_3, or R^1 is bromo, R^2 and R^3 are each hydrogen atom, and R^5 is -C(O)-CH_3, or R^1 is chloro, R^2 and R^5 are each hydrogen atom and R^3 is -N-C(O)-CH_2-O-CH_3, or R^1 is chloro, R^3 is -N-C(O)-para-fluoro-phenyl and R^2 and R^5 are each hydrogen atom, or R^1 and R^3 are each chloro, R^2 is -C(O)-CH_3 and R^5 is hydrogen atom, or R^1 and R^3 are each chloro, R^2 is -C(O)-CH_2-CH_3 and R^5 is hydrogen atom.

17. The use of the compound of the formula I or II as claimed in any one of claims 10 to 16, for the treatment of asthma, osteoarthritis, rheumatoid arthritis (in the case of inflammation), Alzheimer's disease, carcinomatous disorders (potentiation of cytotoxic therapies) and cardiac infarct.

18. A process for the production of a pharmaceutical, which comprises bringing at least one compound of the formula I or II as claimed in any one of claims 10 to 16 into a suitable administration form using a pharmaceutically suitable and physiologically tolerable excipient and, if appropriate, further suitable active compounds, additives or auxiliaries.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 00 10 5514

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	DE 198 07 993 A (BAYER AG) 2 September 1999 (1999-09-02) * claims 1-16 *	1-4	C07D471/04 A61K31/44 //(C07D471/04, 209:00,211:00)
X	WO 98 09625 A (ELI LILLY AND COMPANY) 12 March 1998 (1998-03-12) * claim 1 *	1-4	
X	WO 98 06719 A (BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.) 19 February 1998 (1998-02-19) * claims 1-8 *	1-4	
X	US 5 591 738 A (H. S. LOTSOF) 7 January 1997 (1997-01-07) * claims 1-9 *	1-4	
X	EP 0 705 831 A (BAYER AG) 10 April 1996 (1996-04-10) * claims 1-3 *	1-4	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
X	DE 41 20 109 A (SCHERING AG) 17 December 1992 (1992-12-17) * claim 1 *	1-4	A61K
X	EP 0 667 347 A (ELI LILLY AND COMPANY) 16 August 1995 (1995-08-16) * claims 1-3 *	1-4	
X	PATENT ABSTRACTS OF JAPAN vol. 013, no. 056, 8 February 1989 (1989-02-08) & JP 63 250378 A (MITSUBISHI KASEI CORP.), 18 October 1988 (1988-10-18) * abstract *	1-4	

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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	28 August 2000	Herz, C

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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T : theory or principle underlying the invention
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Application Number
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DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	FR 2 579 207 A (SANOFI) 26 September 1986 (1986-09-26) * claim 1 *	1-4	
X	GB 2 155 462 A (SHELL INTERNATIONALE RESEARCH MAATSCHAPPIJ BV) 25 September 1985 (1985-09-25) * claim 1 *	1-4	
X	PATENT ABSTRACTS OF JAPAN vol. 013, no. 494, 8 November 1989 (1989-11-08) & JP 01 197482 A (MITSUBISHI KASEI CORP.), 9 August 1989 (1989-08-09) * abstract *	1-4	
X	PATENT ABSTRACTS OF JAPAN vol. 009, no. 088, 17 April 1985 (1985-04-17) & JP 59 219229 A (NIPPON SHINYAKU CO., LTD.), 10 December 1984 (1984-12-10) * abstract *	1-4	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
X	DE 32 40 514 A (SCHERING AG) 3 May 1984 (1984-05-03) * claim 1 *	1-4	
X	EP 0 133 000 A (UNIVERSITY OF ILLINOIS) 13 February 1985 (1985-02-13) * claims 1-7 *	1-4	
X	FR 2 516 512 A (J. CORBIERE) 20 May 1983 (1983-05-20) * claim 1 *	1-4	
X	EP 0 017 727 A (CIBA-GEIGY AG) 29 October 1980 (1980-10-29) * claims 1-4 *	1-4	

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The present search report has been drawn up for all claims

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MUNICH	28 August 2000	Herz, C

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D : document cited in the application
L : document cited for other reasons

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EUROPEAN SEARCH REPORT

Application Number
EP 00 10 5514

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	US 5 532 261 A (F. P. DININNO ET AL.) 2 July 1996 (1996-07-02) * Scheme A-L *	1-4	
X	DATABASE WPI Week 198141 Derwent Publications Ltd., London, GB; AN 1981-75256D XP002145945 & SU 797 688 A (LE SANITARNO GIGIENICHESKIJ ME), 23 January 1981 (1981-01-23) * abstract *	1-4	
X	DATABASE WPI Week 197608 Derwent Publications Ltd., London, GB; AN 1976-14482X XP002145946 & SU 469 744 A (AS BIOCHEM. MICROORG.), 8 August 1975 (1975-08-08) * abstract *	1-4	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
X	US 5 514 505 A (W. W. LIMBURG ET AL.) 7 May 1996 (1996-05-07) * column 71, line 39 - column 71, line 38 *	1-4	
X	DE 568 675 C (BOOTS PURE DRUG COMPANY LTD.) 27 January 1933 (1933-01-27) * examples 1-11 *	1-4	
X	US 3 301 867 A (J. SZMUSZKOVICZ) 31 January 1967 (1967-01-31) * claims 2,3 *	1-4	

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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	28 August 2000	Herz, C

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Application Number
EP 00 10 5514

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	DE 10 44 821 B (FARBENFABRIK BAYER AG) 5 April 1957 (1957-04-05) * column 2, line 27 - column 2, line 30 * ---	1-4	
X	US 3 202 670 A (J. SZMUSZKOVICZ) 24 August 1965 (1965-08-24) * claim 1 * ---	1-4	
X	EP 0 110 814 A (SCHERING AG) 13 June 1984 (1984-06-13) * claim 1 * ---	1-4	
X	US 2 759 000 A (C. F. HUEBNER) 14 August 1956 (1956-08-14) * claim 1; examples 5,6 * ---	1-4	
D,Y	US 5 604 236 A (J. A. JAKUBOWSKI, A. D. PALKOWITZ) 18 February 1997 (1997-02-18) * claims 1,2 * ---	1-18	
Y	PATENT ABSTRACTS OF JAPAN vol. 1997, no. 04, 30 April 1997 (1997-04-30) & JP 08 319238 A (ASAHI CHEM. IND. CO., LTD.), 3 December 1996 (1996-12-03) * abstract * ---	1-18	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
A	WO 99 65449 A (SMITHKLINE BEECHAM CORP.) 23 December 1999 (1999-12-23) * claims 1-21 * ---	1-18	
X	J. SAPI ET AL.: "Isoharmine revisited: Thermal rearrangement of a cyanomethyl-2-vinylindole" HETEROCYCLES, vol. 51, no. 2, 1999, pages 361-364, XP000919348 * Scheme 1 * --- -/--	1-4	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
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CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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Application Number
EP 00 10 5514

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	R. KONOWALOWA ET AL.: "Untersuchungen in der Reihe des Harmins und Harmalins. 2. Mitteilung: Nitro- und Aminoderivate des Harmins und Harmalins, O-Alkylether des Harmols und Harmalols" ARCH. PHARM. (WEINHEIM, GER.), vol. 273, 1935, pages 156-163, XP000917794 * page 160 - page 161 *	1-4	
X	W. H. PERKIN JUN., R. ROBINSON: "Harmine and Harmaline" J. CHEM. SOC., vol. 115, 1919, pages 933-972, XP000917608 * entire document *	1-4	
X	A. N. LOMAKIN, I. V. TERENT'EVA: "Mononitro-betacarbolines" CHEM. HETEROCYCL. COMPOUNDS (ENGL. TRANSL.), vol. 4, 1968, pages 756-758, XP000917621 * page 757 *	1-4	
			TECHNICAL FIELDS SEARCHED (Int.Cl.7)
X	CHEM. ZENTRALBL., vol. 72, no. I, 1901, pages 957-959, XP002145944 * page 958 *	1-4	
X	C. E. COULTHARD ET AL.: "The chemotherapy of derivatives of harmine and harmaline. I" BIOCHEM. J., vol. 27, no. 3, 1933, pages 727-739, XP000917474 * table 1 *	1-4	
	-/--		

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	28 August 2000	Herz, C

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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EPO FORM 1503 03.82 (P04C01)

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 00 10 5514

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	E. SPÄTH, E. LEDERER: "Synthesen von 4-Carbolinen" CHEM.BER., vol. 63, 1930, pages 2102-2111, XP000917524 * page 2103 *	1-4	
X	J. W. COOK ET AL.: "The Chemistry of the Mitragyna Genus. Part III. Synthesis of a Degradation Product of Mitragynine" J. CHEM. SOC., 1952, pages 3904-3912, XP000918147 * page 3906 *	1-4	
			TECHNICAL FIELDS SEARCHED (Int.Cl.7)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	28 August 2000	Herz, C

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 00 10 5514

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28-08-2000

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 19807993 A	02-09-1999	NONE	
WO 9809625 A	12-03-1998	AU 4094197 A	26-03-1998
		CA 2236269 A	12-03-1998
		EP 0827746 A	11-03-1998
WO 9806719 A	19-02-1998	EP 0923581 A	23-06-1999
US 5591738 A	07-01-1997	NONE	
EP 705831 A	10-04-1996	DE 4435477 A	11-04-1996
		AU 700609 B	07-01-1999
		AU 3292095 A	18-04-1996
		CA 2159546 A	05-04-1996
		CN 1130631 A,B	11-09-1996
		CZ 9502567 A	17-04-1996
		HR 950505 A	31-08-1997
		HU 73240 A	29-07-1996
		JP 8225526 A	03-09-1996
		NO 953930 A	09-04-1996
		NZ 280130 A	28-05-1996
		PL 310756 A	15-04-1996
		SG 63528 A	30-03-1999
		SK 123995 A	05-06-1996
		US 5684014 A	04-11-1997
		ZA 9508297 A	06-05-1996
DE 4120109 A	17-12-1992	CA 2089569 A	16-12-1992
		WO 9222549 A	23-12-1992
		EP 0543968 A	02-06-1993
		JP 6501956 T	03-03-1994
		PT 100593 A	31-08-1993
		US 5543519 A	06-08-1996
EP 667347 A	16-08-1995	CA 2140722 A	25-07-1995
		JP 7206862 A	08-08-1995
		US 5604236 A	18-02-1997
JP 63250378 A	18-10-1988	NONE	
FR 2579207 A	26-09-1986	DK 132186 A	23-09-1986
		EP 0201366 A	12-11-1986
		FI 861216 A	23-09-1986
		GR 860747 A	21-07-1986
		JP 61275278 A	05-12-1986
		NO 861121 A	23-09-1986

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 00 10 5514

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
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The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

28-08-2000

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR 2579207 A		PT 82243 A,B	01-04-1986
GB 2155462 A	25-09-1985	NONE	
JP 01197482 A	09-08-1989	JP 2579789 B	12-02-1997
JP 59219229 A	10-12-1984	NONE	
DE 3240514 A	03-05-1984	AT 48602 T	15-12-1989
		AU 568513 B	07-01-1988
		AU 2069483 A	03-05-1984
		CA 1260475 A	26-09-1989
		DD 213217 A	05-09-1984
		DE 3380958 D	18-01-1990
		DK 495683 A	30-04-1984
		EP 0110814 A	13-06-1984
		ES 526896 D	01-08-1984
		ES 8406477 A	01-11-1984
		FI 833918 A	30-04-1984
		GR 79637 A	31-10-1984
		HU 198208 B	28-08-1989
		IE 56155 B	08-05-1991
		JP 1909140 C	09-03-1995
		JP 6033260 B	02-05-1994
		JP 59089678 A	23-05-1984
		NO 833942 A	30-04-1984
		NZ 205949 A	31-03-1987
		US 4731358 A	15-03-1988
		ZA 8308072 A	27-06-1984
EP 133000 A	13-02-1985	US 4631149 A	23-12-1986
		DE 3483291 D	31-10-1990
		JP 1814191 C	18-01-1994
		JP 5016428 B	04-03-1993
		JP 60100576 A	04-06-1985
FR 2516512 A	20-05-1983	NONE	
EP 17727 A	29-10-1980	ZA 8001387 A	28-10-1981
		AU 5635580 A	17-09-1981
		DK 72180 A	11-10-1980
		ES 488810 D	16-02-1981
		ES 8103081 A	16-05-1981
		FI 800529 A	11-10-1980
		JP 55143983 A	10-11-1980
		NO 800725 A	13-10-1980

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 00 10 5514

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

28-08-2000

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 5532261	A	02-07-1996	NONE		
SU 797688	A	23-01-1981	NONE		
SU 469744	A	05-05-1975	NONE		
US 5514505	A	07-05-1996	CA	2169980 A	16-11-1996
			EP	0743573 A	20-11-1996
			JP	8314240 A	29-11-1996
DE 568675	C		NONE		
US 3301867	A	31-01-1967	CH	437328 A	
			FR	1565306 A	02-05-1969
			GB	1069717 A	
			NL	6412919 A	07-05-1965
DE 1044821	B		NONE		
US 3202670	A	24-08-1965	NONE		
EP 110814	A	13-06-1984	DE	3240514 A	03-05-1984
			AT	48602 T	15-12-1989
			AU	568513 B	07-01-1988
			AU	2069483 A	03-05-1984
			CA	1260475 A	26-09-1989
			DD	213217 A	05-09-1984
			DE	3380958 D	18-01-1990
			DK	495683 A	30-04-1984
			ES	526896 D	01-08-1984
			ES	8406477 A	01-11-1984
			FI	833918 A	30-04-1984
			GR	79637 A	31-10-1984
			HU	198208 B	28-08-1989
			IE	56155 B	08-05-1991
			JP	1909140 C	09-03-1995
			JP	6033260 B	02-05-1994
			JP	59089678 A	23-05-1984
			NO	833942 A	30-04-1984
			NZ	205949 A	31-03-1987
			US	4731358 A	15-03-1988
			ZA	8308072 A	27-06-1984
US 2759000	A	14-08-1956	NONE		
US 5604236	A	18-02-1997	CA	2140722 A	25-07-1995

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5604236 A		EP 0667347 A JP 7206862 A	16-08-1995 08-08-1995
JP 08319238 A	03-12-1996	NONE	
WO 9965449 A	23-12-1999	AU 4690099 A	05-01-2000

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